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(54) Title: MP53s AS MODIFIERS OF THE p53 PATHWAY AND METHODS OF USE

(57) Abstract: Human MP53 genes are identified as modulators of the p53 pathway, and thus are therapeutic targets for disorders associated with defective p53 function. Methods for identifying modulators of p53, comprising screening for agents that modulate the activity of MP53 are provided.

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**MP53s AS MODIFIERS OF THE p53 PATHWAY AND METHODS OF USE****REFERENCE TO RELATED APPLICATIONS**

This application claims priority to U.S. provisional patent application 60/361,196  
5 filed 3/1/2002. The contents of the prior applications are hereby incorporated in their  
entirety.

**BACKGROUND OF THE INVENTION**

The p53 gene is mutated in over 50 different types of human cancers, including  
10 familial and spontaneous cancers, and is believed to be the most commonly mutated gene  
in human cancer (Zambetti and Levine, FASEB (1993) 7:855-865; Hollstein, *et al.*,  
Nucleic Acids Res. (1994) 22:3551-3555). Greater than 90% of mutations in the p53 gene  
are missense mutations that alter a single amino acid that inactivates p53 function.  
Aberrant forms of human p53 are associated with poor prognosis, more aggressive tumors,  
15 metastasis, and short survival rates (Mitsudomi *et al.*, Clin Cancer Res 2000 Oct;  
6(10):4055-63; Koshland, Science (1993) 262:1953).

The human p53 protein normally functions as a central integrator of signals  
including DNA damage, hypoxia, nucleotide deprivation, and oncogene activation (Prives,  
Cell (1998) 95:5-8). In response to these signals, p53 protein levels are greatly increased  
20 with the result that the accumulated p53 activates cell cycle arrest or apoptosis depending  
on the nature and strength of these signals. Indeed, multiple lines of experimental  
evidence have pointed to a key role for p53 as a tumor suppressor (Levine, Cell (1997)  
88:323-331). For example, homozygous p53 "knockout" mice are developmentally  
normal but exhibit nearly 100% incidence of neoplasia in the first year of life (Donehower  
25 *et al.*, Nature (1992) 356:215-221).

The biochemical mechanisms and pathways through which p53 functions in  
normal and cancerous cells are not fully understood, but one clearly important aspect of  
p53 function is its activity as a gene-specific transcriptional activator. Among the genes  
with known p53-response elements are several with well-characterized roles in either  
30 regulation of the cell cycle or apoptosis, including GADD45, p21/Waf1/Cip1, cyclin G,  
Bax, IGF-BP3, and MDM2 (Levine, Cell (1997) 88:323-331).

The ability to manipulate the genomes of model organisms such as *Drosophila*  
provides a powerful means to analyze biochemical processes that, due to significant  
evolutionary conservation, have direct relevance to more complex vertebrate organisms.

Due to a high level of gene and pathway conservation, the strong similarity of cellular processes, and the functional conservation of genes between these model organisms and mammals, identification of the involvement of novel genes in particular pathways and their functions in such model organisms can directly contribute to the understanding of the correlative pathways and methods of modulating them in mammals (see, for example, 5 Mechler BM et al., 1985 EMBO J 4:1551-1557; Gateff E. 1982 Adv. Cancer Res. 37: 33-74; Watson KL., et al., 1994 J Cell Sci. 18: 19-33; Miklos GL, and Rubin GM. 1996 Cell 86:521-529; Wassarman DA, et al., 1995 Curr Opin Gen Dev 5: 44-50; and Booth DR. 1999 Cancer Metastasis Rev. 18: 261-284). For example, a genetic screen can be carried out in an invertebrate model organism having underexpression (e.g. knockout) or 10 overexpression of a gene (referred to as a "genetic entry point") that yields a visible phenotype. Additional genes are mutated in a random or targeted manner. When a gene mutation changes the original phenotype caused by the mutation in the genetic entry point, the gene is identified as a "modifier" involved in the same or overlapping pathway as the genetic entry point. When the genetic entry point is an ortholog of a human gene 15 implicated in a disease pathway, such as p53, modifier genes can be identified that may be attractive candidate targets for novel therapeutics.

All references cited herein, including patents, patent applications, publications, and sequence information in referenced Genbank identifier numbers, are incorporated herein in 20 their entireties.

## SUMMARY OF THE INVENTION

We have discovered genes that modify the p53 pathway in *Drosophila*, and identified their human orthologs, hereinafter referred to as Modifier of p53 (MP53). The invention provides methods for utilizing these p53 modifier genes and polypeptides to 25 identify MP53-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired p53 function and/or MP53 function. Preferred MP53-modulating agents specifically bind to MP53 polypeptides and restore p53 function. Other preferred MP53-modulating agents are nucleic acid 30 modulators such as antisense oligomers and RNAi that repress MP53 gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA).

MP53 modulating agents may be evaluated by any convenient *in vitro* or *in vivo* assay for molecular interaction with an MP53 polypeptide or nucleic acid. In one

embodiment, candidate MP53 modulating agents are tested with an assay system comprising a MP53 polypeptide or nucleic acid. Agents that produce a change in the activity of the assay system relative to controls are identified as candidate p53 modulating agents. The assay system may be cell-based or cell-free. MP53-modulating agents  
5 include MP53 related proteins (e.g. dominant negative mutants, and biotherapeutics); MP53 -specific antibodies; MP53 -specific antisense oligomers and other nucleic acid modulators; and chemical agents that specifically bind to or interact with MP53 or compete with MP53 binding partner (e.g. by binding to an MP53 binding partner). In one specific embodiment, a small molecule modulator is identified using a binding assay. In  
10 specific embodiments, the screening assay system is selected from an apoptosis assay, a cell proliferation assay, an angiogenesis assay, and a hypoxic induction assay.

In another embodiment, candidate p53 pathway modulating agents are further tested using a second assay system that detects changes in the p53 pathway, such as angiogenic, apoptotic, or cell proliferation changes produced by the originally identified  
15 candidate agent or an agent derived from the original agent. The second assay system may use cultured cells or non-human animals. In specific embodiments, the secondary assay system uses non-human animals, including animals predetermined to have a disease or disorder implicating the p53 pathway, such as an angiogenic, apoptotic, or cell proliferation disorder (e.g. cancer).

20 The invention further provides methods for modulating the MP53 function and/or the p53 pathway in a mammalian cell by contacting the mammalian cell with an agent that specifically binds a MP53 polypeptide or nucleic acid. The agent may be a small molecule modulator, a nucleic acid modulator, or an antibody and may be administered to a mammalian animal predetermined to have a pathology associated the p53 pathway.

25

### DETAILED DESCRIPTION OF THE INVENTION

Genetic screens were designed to identify modifiers of the p53 pathway in *Drosophila*, where a genetic modifier screen was carried out in which p53 was overexpressed in the wing (Ollmann M, et al., Cell 2000 101: 91-101). Modifiers of the  
30 p53 pathway were identified. Accordingly, vertebrate orthologs of these modifiers, and preferably the human orthologs, MP53 genes (i.e., nucleic acids and polypeptides) are attractive drug targets for the treatment of pathologies associated with a defective p53 signaling pathway, such as cancer. Table 1 (Example II) lists the modifiers and their orthologs.



In vitro and in vivo methods of assessing MP53 function are provided herein. Modulation of the MP53 or their respective binding partners is useful for understanding the association of the p53 pathway and its members in normal and disease conditions and for developing diagnostics and therapeutic modalities for p53 related pathologies. MP53-  
5 modulating agents that act by inhibiting or enhancing MP53 expression, directly or indirectly, for example, by affecting an MP53 function such as enzymatic (e.g., catalytic) or binding activity, can be identified using methods provided herein. MP53 modulating agents are useful in diagnosis, therapy and pharmaceutical development.

10 **Nucleic acids and polypeptides of the invention**

Sequences related to MP53 nucleic acids and polypeptides that can be used in the invention are disclosed in Genbank (referenced by Genbank identifier (GI) or RefSeq number), and shown in Table 1 (ExampleII).

The term "MP53 polypeptide" refers to a full-length MP53 protein or a  
15 functionally active fragment or derivative thereof. A "functionally active" MP53 fragment or derivative exhibits one or more functional activities associated with a full-length, wild-type MP53 protein, such as antigenic or immunogenic activity, enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of MP53 proteins, derivatives and fragments can be assayed by various methods known to one skilled in the  
20 art (Current Protocols in Protein Science (1998) Coligan *et al.*, eds., John Wiley & Sons, Inc., Somerset, New Jersey) and as further discussed below. In one embodiment, a functionally active MP53 polypeptide is a MP53 derivative capable of rescuing defective endogenous MP53 activity, such as in cell based or animal assays; the rescuing derivative may be from the same or a different species. For purposes herein, functionally active  
25 fragments also include those fragments that comprise one or more structural domains of an MP53, such as a binding domain. Protein domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res, 1999, 27:260-2). Methods for obtaining MP53 polypeptides are also further described below. In some embodiments, preferred fragments are functionally active, domain-containing fragments comprising at least 25  
30 contiguous amino acids, preferably at least 50, more preferably 75, and most preferably at least 100 contiguous amino acids of any one of SEQ ID NOs:57-112 (an MP53). In further preferred embodiments, the fragment comprises the entire functionally active domain.

The term "MP53 nucleic acid" refers to a DNA or RNA molecule that encodes a MP53 polypeptide. Preferably, the MP53 polypeptide or nucleic acid or fragment thereof is from a human, but can also be an ortholog, or derivative thereof with at least 70% sequence identity, preferably at least 80%, more preferably 85%, still more preferably 90%, and most preferably at least 95% sequence identity with human MP53. Methods of identifying orthologs are known in the art. Normally, orthologs in different species retain the same function, due to presence of one or more protein motifs and/or 3-dimensional structures. Orthologs are generally identified by sequence homology analysis, such as BLAST analysis, usually using protein bait sequences. Sequences are assigned as a potential ortholog if the best hit sequence from the forward BLAST result retrieves the original query sequence in the reverse BLAST (Huynen MA and Bork P, Proc Natl Acad Sci (1998) 95:5849-5856; Huynen MA *et al.*, Genome Research (2000) 10:1204-1210). Programs for multiple sequence alignment, such as CLUSTAL (Thompson JD et al, 1994, Nucleic Acids Res 22:4673-4680) may be used to highlight conserved regions and/or residues of orthologous proteins and to generate phylogenetic trees. In a phylogenetic tree representing multiple homologous sequences from diverse species (e.g., retrieved through BLAST analysis), orthologous sequences from two species generally appear closest on the tree with respect to all other sequences from these two species. Structural threading or other analysis of protein folding (e.g., using software by ProCeryon, Biosciences, Salzburg, Austria) may also identify potential orthologs. In evolution, when a gene duplication event follows speciation, a single gene in one species, such as *Drosophila*, may correspond to multiple genes (paralogs) in another, such as human. As used herein, the term "orthologs" encompasses paralogs. As used herein, "percent (%) sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410) with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A % identity value is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is

being reported. "Percent (%) amino acid sequence similarity" is determined by doing the same calculation as for determining % amino acid sequence identity, but including conservative amino acid substitutions in addition to identical amino acids in the computation.

5           A conservative amino acid substitution is one in which an amino acid is substituted for another amino acid having similar properties such that the folding or activity of the protein is not significantly affected. Aromatic amino acids that can be substituted for each other are phenylalanine, tryptophan, and tyrosine; interchangeable hydrophobic amino acids are leucine, isoleucine, methionine, and valine; interchangeable polar amino acids  
10   are glutamine and asparagine; interchangeable basic amino acids are arginine, lysine and histidine; interchangeable acidic amino acids are aspartic acid and glutamic acid; and interchangeable small amino acids are alanine, serine, threonine, cysteine and glycine.

          Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, *Advances in*  
15 *Applied Mathematics* 2:482-489; database: European Bioinformatics Institute; Smith and Waterman, 1981, *J. of Molec.Biol.*, 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" ([www.psc.edu](http://www.psc.edu)) and references cited therein.; W.R. Pearson, 1991, *Genomics* 11:635-650). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff  
20 (Dayhoff: *Atlas of Protein Sequences and Structure*, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized by Gribskov (Gribskov 1986 *Nucl. Acids Res.* 14(6):6745-6763). The Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated, the  
25 "Match" value reflects "sequence identity."

          Derivative nucleic acid molecules of the subject nucleic acid molecules include sequences that hybridize to the nucleic acid sequence of any of SEQ ID NOs:1-56. The stringency of hybridization can be controlled by temperature, ionic strength, pH, and the presence of denaturing agents such as formamide during hybridization and washing.  
30   Conditions routinely used are set out in readily available procedure texts (*e.g.*, *Current Protocol in Molecular Biology*, Vol. 1, Chap. 2.10, John Wiley & Sons, Publishers (1994); Sambrook *et al.*, *Molecular Cloning*, Cold Spring Harbor (1989)). In some embodiments, a nucleic acid molecule of the invention is capable of hybridizing to a nucleic acid molecule containing the nucleotide sequence of any one of SEQ ID NOs:1-56 under high

stringency hybridization conditions that are: prehybridization of filters containing nucleic acid for 8 hours to overnight at 65° C in a solution comprising 6X single strength citrate (SSC) (1X SSC is 0.15 M NaCl, 0.015 M Na citrate; pH 7.0), 5X Denhardt's solution, 0.05% sodium pyrophosphate and 100 µg/ml herring sperm DNA; hybridization for 18-20  
5 hours at 65° C in a solution containing 6X SSC, 1X Denhardt's solution, 100 µg/ml yeast tRNA and 0.05% sodium pyrophosphate; and washing of filters at 65° C for 1h in a solution containing 0.1X SSC and 0.1% SDS (sodium dodecyl sulfate).

In other embodiments, moderately stringent hybridization conditions are used that are: pretreatment of filters containing nucleic acid for 6 h at 40° C in a solution containing  
10 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 µg/ml denatured salmon sperm DNA; hybridization for 18-20h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 µg/ml salmon sperm DNA, and 10% (wt/vol) dextran sulfate; followed by washing twice for 1 hour at 55° C in a solution  
15 containing 2X SSC and 0.1% SDS.

Alternatively, low stringency conditions can be used that are: incubation for 8 hours to overnight at 37° C in a solution comprising 20% formamide, 5 x SSC, 50 mM sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured sheared salmon sperm DNA; hybridization in the same buffer for 18 to 20  
20 hours; and washing of filters in 1 x SSC at about 37° C for 1 hour.

### **Isolation, Production, Expression, and Mis-expression of MP53 Nucleic Acids and Polypeptides**

MP53 nucleic acids and polypeptides, useful for identifying and testing agents that  
25 modulate MP53 function and for other applications related to the involvement of MP53 in the p53 pathway. MP53 nucleic acids and derivatives and orthologs thereof may be obtained using any available method. For instance, techniques for isolating cDNA or genomic DNA sequences of interest by screening DNA libraries or by using polymerase chain reaction (PCR) are well known in the art. In general, the particular use for the  
30 protein will dictate the particulars of expression, production, and purification methods. For instance, production of proteins for use in screening for modulating agents may require methods that preserve specific biological activities of these proteins, whereas production of proteins for antibody generation may require structural integrity of particular epitopes. Expression of proteins to be purified for screening or antibody production may

require the addition of specific tags (*e.g.*, generation of fusion proteins). Overexpression of an MP53 protein for assays used to assess MP53 function, such as involvement in cell cycle regulation or hypoxic response, may require expression in eukaryotic cell lines capable of these cellular activities. Techniques for the expression, production, and purification of proteins are well known in the art; any suitable means therefore may be used (*e.g.*, Higgins SJ and Hames BD (eds.) *Protein Expression: A Practical Approach*, Oxford University Press Inc., New York 1999; Stanbury PF et al., *Principles of Fermentation Technology*, 2<sup>nd</sup> edition, Elsevier Science, New York, 1995; Doonan S (ed.) *Protein Purification Protocols*, Humana Press, New Jersey, 1996; Coligan JE et al, *Current Protocols in Protein Science* (eds.), 1999, John Wiley & Sons, New York). In particular embodiments, recombinant MP53 is expressed in a cell line known to have defective p53 function (*e.g.* SAOS-2 osteoblasts, H1299 lung cancer cells, C33A and HT3 cervical cancer cells, HT-29 and DLD-1 colon cancer cells, among others, available from American Type Culture Collection (ATCC), Manassas, VA). The recombinant cells are used in cell-based screening assay systems of the invention, as described further below.

The nucleotide sequence encoding an MP53 polypeptide can be inserted into any appropriate expression vector. The necessary transcriptional and translational signals, including promoter/enhancer element, can derive from the native MP53 gene and/or its flanking regions or can be heterologous. A variety of host-vector expression systems may be utilized, such as mammalian cell systems infected with virus (*e.g.* vaccinia virus, adenovirus, *etc.*); insect cell systems infected with virus (*e.g.* baculovirus); microorganisms such as yeast containing yeast vectors, or bacteria transformed with bacteriophage, plasmid, or cosmid DNA. An isolated host cell strain that modulates the expression of, modifies, and/or specifically processes the gene product may be used.

To detect expression of the MP53 gene product, the expression vector can comprise a promoter operably linked to an MP53 gene nucleic acid, one or more origins of replication, and, one or more selectable markers (*e.g.* thymidine kinase activity, resistance to antibiotics, *etc.*). Alternatively, recombinant expression vectors can be identified by assaying for the expression of the MP53 gene product based on the physical or functional properties of the MP53 protein in *in vitro* assay systems (*e.g.* immunoassays).

The MP53 protein, fragment, or derivative may be optionally expressed as a fusion, or chimeric protein product (*i.e.* it is joined via a peptide bond to a heterologous protein sequence of a different protein), for example to facilitate purification or detection. A chimeric product can be made by ligating the appropriate nucleic acid sequences

encoding the desired amino acid sequences to each other using standard methods and expressing the chimeric product. A chimeric product may also be made by protein synthetic techniques, *e.g.* by use of a peptide synthesizer (Hunkapiller *et al.*, Nature (1984) 310:105-111).

5           Once a recombinant cell that expresses the MP53 gene sequence is identified, the gene product can be isolated and purified using standard methods (*e.g.* ion exchange, affinity, and gel exclusion chromatography; centrifugation; differential solubility; electrophoresis). Alternatively, native MP53 proteins can be purified from natural  
10           sources, by standard methods (*e.g.* immunoaffinity purification). Once a protein is obtained, it may be quantified and its activity measured by appropriate methods, such as immunoassay, bioassay, or other measurements of physical properties, such as crystallography.

          The methods of this invention may also use cells that have been engineered for altered expression (mis-expression) of MP53 or other genes associated with the p53  
15           pathway. As used herein, mis-expression encompasses ectopic expression, over-expression, under-expression, and non-expression (*e.g.* by gene knock-out or blocking expression that would otherwise normally occur).

#### **Genetically modified animals**

20           Animal models that have been genetically modified to alter MP53 expression may be used in *in vivo* assays to test for activity of a candidate p53 modulating agent, or to further assess the role of MP53 in a p53 pathway process such as apoptosis or cell proliferation. Preferably, the altered MP53 expression results in a detectable phenotype, such as decreased or increased levels of cell proliferation, angiogenesis, or apoptosis  
25           compared to control animals having normal MP53 expression. The genetically modified animal may additionally have altered p53 expression (*e.g.* p53 knockout). Preferred genetically modified animals are mammals such as primates, rodents (preferably mice or rats), among others. Preferred non-mammalian species include zebrafish, *C. elegans*, and *Drosophila*. Preferred genetically modified animals are transgenic animals having a  
30           heterologous nucleic acid sequence present as an extrachromosomal element in a portion of its cells, *i.e.* mosaic animals (see, for example, techniques described by Jakobovits, 1994, Curr. Biol. 4:761-763.) or stably integrated into its germ line DNA (*i.e.*, in the genomic sequence of most or all of its cells). Heterologous nucleic acid is introduced into

the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal.

Methods of making transgenic animals are well-known in the art (for transgenic mice see Brinster et al., Proc. Nat. Acad. Sci. USA 82: 4438-4442 (1985), U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder et al., U.S. Pat. No. 4,873,191 by Wagner et al., and Hogan, B., Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); for particle bombardment see U.S. Pat. No., 4,945,050, by Sandford *et al.*; for transgenic *Drosophila* see Rubin and Spradling, Science (1982) 218:348-53 and U.S. Pat. No. 4,670,388; for transgenic insects see Berghammer A.J. *et al.*, A Universal Marker for Transgenic Insects (1999) Nature 402:370-371; for transgenic Zebrafish see Lin S., Transgenic Zebrafish, Methods Mol Biol. (2000);136:375-3830); for microinjection procedures for fish, amphibian eggs and birds see Houdebine and Chourrout, Experientia (1991) 47:897-905; for transgenic rats see Hammer *et al.*, Cell (1990) 63:1099-1112; and for culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection see, e.g., Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E. J. Robertson, ed., IRL Press (1987)). Clones of the nonhuman transgenic animals can be produced according to available methods (see Wilmut, I. *et al.* (1997) Nature 385:810-813; and PCT International Publication Nos. WO 97/07668 and WO 97/07669).

In one embodiment, the transgenic animal is a "knock-out" animal having a heterozygous or homozygous alteration in the sequence of an endogenous MP53 gene that results in a decrease of MP53 function, preferably such that MP53 expression is undetectable or insignificant. Knock-out animals are typically generated by homologous recombination with a vector comprising a transgene having at least a portion of the gene to be knocked out. Typically a deletion, addition or substitution has been introduced into the transgene to functionally disrupt it. The transgene can be a human gene (e.g., from a human genomic clone) but more preferably is an ortholog of the human gene derived from the transgenic host species. For example, a mouse MP53 gene is used to construct a homologous recombination vector suitable for altering an endogenous MP53 gene in the mouse genome. Detailed methodologies for homologous recombination in mice are available (see Capecchi, Science (1989) 244:1288-1292; Joyner *et al.*, Nature (1989) 338:153-156). Procedures for the production of non-rodent transgenic mammals and other animals are also available (Houdebine and Chourrout, *supra*; Pursel *et al.*, Science (1989)

244:1281-1288; Simms *et al.*, Bio/Technology (1988) 6:179-183). In a preferred embodiment, knock-out animals, such as mice harboring a knockout of a specific gene, may be used to produce antibodies against the human counterpart of the gene that has been knocked out (Claesson MH *et al.*, (1994) Scan J Immunol 40:257-264; Declerck PJ *et al.*, (1995) J Biol Chem. 270:8397-400).

In another embodiment, the transgenic animal is a "knock-in" animal having an alteration in its genome that results in altered expression (e.g., increased (including ectopic) or decreased expression) of the MP53 gene, e.g., by introduction of additional copies of MP53, or by operatively inserting a regulatory sequence that provides for altered expression of an endogenous copy of the MP53 gene. Such regulatory sequences include inducible, tissue-specific, and constitutive promoters and enhancer elements. The knock-in can be homozygous or heterozygous.

Transgenic nonhuman animals can also be produced that contain selected systems allowing for regulated expression of the transgene. One example of such a system that may be produced is the cre/loxP recombinase system of bacteriophage P1 (Lakso *et al.*, PNAS (1992) 89:6232-6236; U.S. Pat. No. 4,959,317). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) Science 251:1351-1355; U.S. Pat. No. 5,654,182). In a preferred embodiment, both Cre-LoxP and Flp-Frt are used in the same system to regulate expression of the transgene, and for sequential deletion of vector sequences in the same cell (Sun X *et al.* (2000) Nat Genet 25:83-6).

The genetically modified animals can be used in genetic studies to further elucidate the p53 pathway, as animal models of disease and disorders implicating defective p53 function, and for *in vivo* testing of candidate therapeutic agents, such as those identified in screens described below. The candidate therapeutic agents are administered to a genetically modified animal having altered MP53 function and phenotypic changes are compared with appropriate control animals such as genetically modified animals that receive placebo treatment, and/or animals with unaltered MP53 expression that receive candidate therapeutic agent.



In addition to the above-described genetically modified animals having altered MP53 function, animal models having defective p53 function (and otherwise normal MP53 function), can be used in the methods of the present invention. For example, a p53 knockout mouse can be used to assess, *in vivo*, the activity of a candidate p53 modulating agent identified in one of the *in vitro* assays described below. p53 knockout mice are described in the literature (Jacks et al., Nature 2001;410:1111-1116, 1043-1044; Donehower *et al.*, supra). Preferably, the candidate p53 modulating agent when administered to a model system with cells defective in p53 function, produces a detectable phenotypic change in the model system indicating that the p53 function is restored, i.e., the cells exhibit normal cell cycle progression.

### **Modulating Agents**

The invention provides methods to identify agents that interact with and/or modulate the function of MP53 and/or the p53 pathway. Modulating agents identified by the methods are also part of the invention. Such agents are useful in a variety of diagnostic and therapeutic applications associated with the p53 pathway, as well as in further analysis of the MP53 protein and its contribution to the p53 pathway. Accordingly, the invention also provides methods for modulating the p53 pathway comprising the step of specifically modulating MP53 activity by administering a MP53-interacting or -modulating agent.

As used herein, an "MP53-modulating agent" is any agent that modulates MP53 function, for example, an agent that interacts with MP53 to inhibit or enhance MP53 activity or otherwise affect normal MP53 function. MP53 function can be affected at any level, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In a preferred embodiment, the MP53 - modulating agent specifically modulates the function of the MP53. The phrases "specific modulating agent", "specifically modulates", etc., are used herein to refer to modulating agents that directly bind to the MP53 polypeptide or nucleic acid, and preferably inhibit, enhance, or otherwise alter, the function of the MP53. These phrases also encompass modulating agents that alter the interaction of the MP53 with a binding partner, substrate, or cofactor (e.g. by binding to a binding partner of an MP53, or to a protein/binding partner complex, and altering MP53 function). In a further preferred embodiment, the MP53- modulating agent is a modulator of the p53 pathway (e.g. it restores and/or upregulates p53 function) and thus is also a p53-modulating agent.

Preferred MP53-modulating agents include small molecule compounds; MP53-interacting proteins, including antibodies and other biotherapeutics; and nucleic acid modulators such as antisense and RNA inhibitors. The modulating agents may be formulated in pharmaceutical compositions, for example, as compositions that may  
5 comprise other active ingredients, as in combination therapy, and/or suitable carriers or excipients. Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, 19<sup>th</sup> edition.

#### 10           **Small molecule modulators**

Small molecules are often preferred to modulate function of proteins with enzymatic function, and/or containing protein interaction domains. Chemical agents, referred to in the art as "small molecule" compounds are typically organic, non-peptide molecules, having a molecular weight less than 10,000, preferably less than 5,000, more  
15 preferably less than 1,000, and most preferably less than 500. This class of modulators includes chemically synthesized molecules, for instance, compounds from combinatorial chemical libraries. Synthetic compounds may be rationally designed or identified based on known or inferred properties of the MP53 protein or may be identified by screening compound libraries. Alternative appropriate modulators of this class are natural products,  
20 particularly secondary metabolites from organisms such as plants or fungi, which can also be identified by screening compound libraries for MP53-modulating activity. Methods for generating and obtaining compounds are well known in the art (Schreiber SL, Science (2000) 151: 1964-1969; Radmann J and Gunther J, Science (2000) 151:1947-1948).

Small molecule modulators identified from screening assays, as described below,  
25 can be used as lead compounds from which candidate clinical compounds may be designed, optimized, and synthesized. Such clinical compounds may have utility in treating pathologies associated with the p53 pathway. The activity of candidate small molecule modulating agents may be improved several-fold through iterative secondary functional validation, as further described below, structure determination, and candidate  
30 modulator modification and testing. Additionally, candidate clinical compounds are generated with specific regard to clinical and pharmacological properties. For example, the reagents may be derivatized and re-screened using *in vitro* and *in vivo* assays to optimize activity and minimize toxicity for pharmaceutical development.

### Protein Modulators

Specific MP53-interacting proteins are useful in a variety of diagnostic and therapeutic applications related to the p53 pathway and related disorders, as well as in validation assays for other MP53-modulating agents. In a preferred embodiment, MP53-interacting proteins affect normal MP53 function, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In another embodiment, MP53-interacting proteins are useful in detecting and providing information about the function of MP53 proteins, as is relevant to p53 related disorders, such as cancer (e.g., for diagnostic means).

10 An MP53-interacting protein may be endogenous, i.e. one that naturally interacts genetically or biochemically with an MP53, such as a member of the MP53 pathway that modulates MP53 expression, localization, and/or activity. MP53-modulators include dominant negative forms of MP53-interacting proteins and of MP53 proteins themselves. Yeast two-hybrid and variant screens offer preferred methods for identifying endogenous MP53-interacting proteins (Finley, R. L. et al. (1996) in DNA Cloning-Expression Systems: A Practical Approach, eds. Glover D. & Hames B. D (Oxford University Press, Oxford, England), pp. 169-203; Fashema SF et al., Gene (2000) 250:1-14; Drees BL Curr Opin Chem Biol (1999) 3:64-70; Vidal M and Legrain P Nucleic Acids Res (1999) 27:919-29; and U.S. Pat. No. 5,928,868). Mass spectrometry is an alternative preferred method for the elucidation of protein complexes (reviewed in, e.g., Pandley A and Mann M, Nature (2000) 405:837-846; Yates JR 3<sup>rd</sup>, Trends Genet (2000) 16:5-8).

An MP53-interacting protein may be an exogenous protein, such as an MP53-specific antibody or a T-cell antigen receptor (see, e.g., Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; Harlow and Lane (1999) Using antibodies: a laboratory manual. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press). MP53 antibodies are further discussed below.

In preferred embodiments, an MP53-interacting protein specifically binds an MP53 protein. In alternative preferred embodiments, an MP53-modulating agent binds an MP53 substrate, binding partner, or cofactor.

30

### *Antibodies*

In another embodiment, the protein modulator is an MP53 specific antibody agonist or antagonist. The antibodies have therapeutic and diagnostic utilities, and can be used in screening assays to identify MP53 modulators. The antibodies can also be used in

dissecting the portions of the MP53 pathway responsible for various cellular responses and in the general processing and maturation of the MP53.

Antibodies that specifically bind MP53 polypeptides can be generated using known methods. Preferably the antibody is specific to a mammalian ortholog of MP53 polypeptide, and more preferably, to human MP53. Antibodies may be polyclonal,  
5 monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')<sub>2</sub> fragments, fragments produced by a FAb expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. Epitopes of MP53 which are particularly antigenic can be selected, for example, by routine  
10 screening of MP53 polypeptides for antigenicity or by applying a theoretical method for selecting antigenic regions of a protein (Hopp and Wood (1981), Proc. Natl. Acad. Sci. U.S.A. 78:3824-28; Hopp and Wood, (1983) Mol. Immunol. 20:483-89; Sutcliffe et al., (1983) Science 219:660-66) to the amino acid sequence of any of SEQ ID NOs:57-112. Monoclonal antibodies with affinities of  $10^8 \text{ M}^{-1}$  preferably  $10^9 \text{ M}^{-1}$  to  $10^{10} \text{ M}^{-1}$ , or  
15 stronger can be made by standard procedures as described (Harlow and Lane, *supra*; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York; and U.S. Pat. Nos. 4,381,292; 4,451,570; and 4,618,577). Antibodies may be generated against crude cell extracts of MP53 or substantially purified fragments thereof. If MP53 fragments are used, they preferably comprise at least 10, and more preferably, at  
20 least 20 contiguous amino acids of an MP53 protein. In a particular embodiment, MP53-specific antigens and/or immunogens are coupled to carrier proteins that stimulate the immune response. For example, the subject polypeptides are covalently coupled to the keyhole limpet hemocyanin (KLH) carrier, and the conjugate is emulsified in Freund's complete adjuvant, which enhances the immune response. An appropriate immune system  
25 such as a laboratory rabbit or mouse is immunized according to conventional protocols.

The presence of MP53-specific antibodies is assayed by an appropriate assay such as a solid phase enzyme-linked immunosorbant assay (ELISA) using immobilized corresponding MP53 polypeptides. Other assays, such as radioimmunoassays or fluorescent assays might also be used.

30 Chimeric antibodies specific to MP53 polypeptides can be made that contain different portions from different animal species. For instance, a human immunoglobulin constant region may be linked to a variable region of a murine mAb, such that the antibody derives its biological activity from the human antibody, and its binding specificity from the murine fragment. Chimeric antibodies are produced by splicing

together genes that encode the appropriate regions from each species (Morrison et al., Proc. Natl. Acad. Sci. (1984) 81:6851-6855; Neuberger et al., Nature (1984) 312:604-608; Takeda et al., Nature (1985) 31:452-454). Humanized antibodies, which are a form of chimeric antibodies, can be generated by grafting complementary-determining regions (CDRs) (Carlos, T. M., J. M. Harlan. 1994. Blood 84:2068-2101) of mouse antibodies into a background of human framework regions and constant regions by recombinant DNA technology (Riechmann LM, et al., 1988 Nature 323: 323-327). Humanized antibodies contain ~10% murine sequences and ~90% human sequences, and thus further reduce or eliminate immunogenicity, while retaining the antibody specificities (Co MS, and Queen C. 1991 Nature 351: 501-501; Morrison SL. 1992 Ann. Rev. Immun. 10:239-265). Humanized antibodies and methods of their production are well-known in the art (U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370).

MP53-specific single chain antibodies which are recombinant, single chain polypeptides formed by linking the heavy and light chain fragments of the Fv regions via an amino acid bridge, can be produced by methods known in the art (U.S. Pat. No. 4,946,778; Bird, Science (1988) 242:423-426; Huston et al., Proc. Natl. Acad. Sci. USA (1988) 85:5879-5883; and Ward et al., Nature (1989) 334:544-546).

Other suitable techniques for antibody production involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors (Huse et al., Science (1989) 246:1275-1281). As used herein, T-cell antigen receptors are included within the scope of antibody modulators (Harlow and Lane, 1988, *supra*).

The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, antibodies will be labeled by joining, either covalently or non-covalently, a substance that provides for a detectable signal, or that is toxic to cells that express the targeted protein (Menard S, et al., Int J. Biol Markers (1989) 4:131-134). A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, fluorescent emitting lanthanide metals, chemiluminescent moieties, bioluminescent moieties, magnetic particles, and the like (U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241). Also, recombinant immunoglobulins may be produced (U.S. Pat. No. 4,816,567). Antibodies to cytoplasmic polypeptides may

be delivered and reach their targets by conjugation with membrane-penetrating toxin proteins (U.S. Pat. No. 6,086,900).

When used therapeutically in a patient, the antibodies of the subject invention are typically administered parenterally, when possible at the target site, or intravenously. The therapeutically effective dose and dosage regimen is determined by clinical studies. Typically, the amount of antibody administered is in the range of about 0.1 mg/kg –to about 10 mg/kg of patient weight. For parenteral administration, the antibodies are formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable vehicle. Such vehicles are inherently nontoxic and non-therapeutic. Examples are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Nonaqueous vehicles such as fixed oils, ethyl oleate, or liposome carriers may also be used. The vehicle may contain minor amounts of additives, such as buffers and preservatives, which enhance isotonicity and chemical stability or otherwise enhance therapeutic potential. The antibodies' concentrations in such vehicles are typically in the range of about 1 mg/ml to about 10 mg/ml. Immunotherapeutic methods are further described in the literature (US Pat. No. 5,859,206; WO0073469).

#### *Specific biotherapeutics*

In a preferred embodiment, an MP53-interacting protein may have biotherapeutic applications. Biotherapeutic agents formulated in pharmaceutically acceptable carriers and dosages may be used to activate or inhibit signal transduction pathways. This modulation may be accomplished by binding a ligand, thus inhibiting the activity of the pathway; or by binding a receptor, either to inhibit activation of, or to activate, the receptor. Alternatively, the biotherapeutic may itself be a ligand capable of activating or inhibiting a receptor. Biotherapeutic agents and methods of producing them are described in detail in U.S. Pat. No. 6,146,628.

When the MP53 is a ligand, it may be used as a biotherapeutic agent to activate or inhibit its natural receptor. Alternatively, antibodies against MP53, as described in the previous section, may be used as biotherapeutic agents.

When the MP53 is a receptor, its ligand(s), antibodies to the ligand(s) or the MP53 itself may be used as biotherapeutics to modulate the activity of MP53 in the p53 pathway.

### Nucleic Acid Modulators

Other preferred MP53-modulating agents comprise nucleic acid molecules, such as antisense oligomers or double stranded RNA (dsRNA), which generally inhibit MP53 activity. Preferred nucleic acid modulators interfere with the function of the MP53 nucleic acid such as DNA replication, transcription, translocation of the MP53 RNA to the site of protein translation, translation of protein from the MP53 RNA, splicing of the MP53 RNA to yield one or more mRNA species, or catalytic activity which may be engaged in or facilitated by the MP53 RNA.

In one embodiment, the antisense oligomer is an oligonucleotide that is sufficiently complementary to an MP53 mRNA to bind to and prevent translation, preferably by binding to the 5' untranslated region. MP53-specific antisense oligonucleotides, preferably range from at least 6 to about 200 nucleotides. In some embodiments the oligonucleotide is preferably at least 10, 15, or 20 nucleotides in length. In other embodiments, the oligonucleotide is preferably less than 50, 40, or 30 nucleotides in length. The oligonucleotide can be DNA or RNA or a chimeric mixture or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents that facilitate transport across the cell membrane, hybridization-triggered cleavage agents, and intercalating agents.

In another embodiment, the antisense oligomer is a phosphothioate morpholino oligomer (PMO). PMOs are assembled from four different morpholino subunits, each of which contain one of four genetic bases (A, C, G, or T) linked to a six-membered morpholine ring. Polymers of these subunits are joined by non-ionic phosphodiamidate intersubunit linkages. Details of how to make and use PMOs and other antisense oligomers are well known in the art (e.g. see WO99/18193; Probst JC, Antisense Oligodeoxynucleotide and Ribozyme Design, Methods. (2000) 22(3):271-281; Summerton J, and Weller D. 1997 Antisense Nucleic Acid Drug Dev. :7:187-95; US Pat. No. 5,235,033; and US Pat No. 5,378,841).

Alternative preferred MP53 nucleic acid modulators are double-stranded RNA species mediating RNA interference (RNAi). RNAi is the process of sequence-specific, post-transcriptional gene silencing in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. Methods relating to the use of RNAi to silence genes in *C. elegans*, *Drosophila*, plants, and humans are known

in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); Sharp, P. A. RNA interference 2001. Genes Dev. 15, 485-490 (2001); Hammond, S. M., et al., Nature Rev. Genet. 2, 110-1119 (2001); Tuschl, T. Chem. Biochem. 2, 239-245 (2001); Hamilton, A. et al., Science 286, 950-952 (1999); Hammond, S. M., et al.,  
5 Nature 404, 293-296 (2000); Zamore, P. D., et al., Cell 101, 25-33 (2000); Bernstein, E., et al., Nature 409, 363-366 (2001); Elbashir, S. M., et al., Genes Dev. 15, 188-200 (2001); WO0129058; WO9932619; Elbashir SM, et al., 2001 Nature 411:494-498).

Nucleic acid modulators are commonly used as research reagents, diagnostics, and therapeutics. For example, antisense oligonucleotides, which are able to inhibit gene  
10 expression with exquisite specificity, are often used to elucidate the function of particular genes (see, for example, U.S. Pat. No. 6,165,790). Nucleic acid modulators are also used, for example, to distinguish between functions of various members of a biological pathway. For example, antisense oligomers have been employed as therapeutic moieties in the treatment of disease states in animals and man and have been demonstrated in numerous  
15 clinical trials to be safe and effective (Milligan JF, *et al*, Current Concepts in Antisense Drug Design, J Med Chem. (1993) 36:1923-1937; Tonkinson JL *et al.*, Antisense Oligodeoxynucleotides as Clinical Therapeutic Agents, Cancer Invest. (1996) 14:54-65). Accordingly, in one aspect of the invention, an MP53-specific nucleic acid modulator is used in an assay to further elucidate the role of the MP53 in the p53 pathway, and/or its  
20 relationship to other members of the pathway. In another aspect of the invention, an MP53-specific antisense oligomer is used as a therapeutic agent for treatment of p53-related disease states.

### Assay Systems

25 The invention provides assay systems and screening methods for identifying specific modulators of MP53 activity. As used herein, an "assay system" encompasses all the components required for performing and analyzing results of an assay that detects and/or measures a particular event. In general, primary assays are used to identify or confirm a modulator's specific biochemical or molecular effect with respect to the MP53  
30 nucleic acid or protein. In general, secondary assays further assess the activity of a MP53 modulating agent identified by a primary assay and may confirm that the modulating agent affects MP53 in a manner relevant to the p53 pathway. In some cases, MP53 modulators will be directly tested in a secondary assay.



In a preferred embodiment, the screening method comprises contacting a suitable assay system comprising an MP53 polypeptide or nucleic acid with a candidate agent under conditions whereby, but for the presence of the agent, the system provides a reference activity (e.g. binding activity), which is based on the particular molecular event the screening method detects. A statistically significant difference between the agent-biased activity and the reference activity indicates that the candidate agent modulates MP53 activity, and hence the p53 pathway. The MP53 polypeptide or nucleic acid used in the assay may comprise any of the nucleic acids or polypeptides described above.

## Primary Assays

The type of modulator tested generally determines the type of primary assay.

### *Primary assays for small molecule modulators*

For small molecule modulators, screening assays are used to identify candidate modulators. Screening assays may be cell-based or may use a cell-free system that recreates or retains the relevant biochemical reaction of the target protein (reviewed in Sittampalam GS *et al.*, Curr Opin Chem Biol (1997) 1:384-91 and accompanying references). As used herein the term "cell-based" refers to assays using live cells, dead cells, or a particular cellular fraction, such as a membrane, endoplasmic reticulum, or mitochondrial fraction. The term "cell free" encompasses assays using substantially purified protein (either endogenous or recombinantly produced), partially purified or crude cellular extracts. Screening assays may detect a variety of molecular events, including protein-DNA interactions, protein-protein interactions (e.g., receptor-ligand binding), transcriptional activity (e.g., using a reporter gene), enzymatic activity (e.g., via a property of the substrate), activity of second messengers, immunogenicity and changes in cellular morphology or other cellular characteristics. Appropriate screening assays may use a wide range of detection methods including fluorescent, radioactive, colorimetric, spectrophotometric, and amperometric methods, to provide a read-out for the particular molecular event detected.

Cell-based screening assays usually require systems for recombinant expression of MP53 and any auxiliary proteins demanded by the particular assay. Appropriate methods for generating recombinant proteins produce sufficient quantities of proteins that retain their relevant biological activities and are of sufficient purity to optimize activity and assure assay reproducibility. Yeast two-hybrid and variant screens, and mass spectrometry

provide preferred methods for determining protein-protein interactions and elucidation of protein complexes. In certain applications, when MP53-interacting proteins are used in screens to identify small molecule modulators, the binding specificity of the interacting protein to the MP53 protein may be assayed by various known methods such as substrate processing (e.g. ability of the candidate MP53-specific binding agents to function as negative effectors in MP53-expressing cells), binding equilibrium constants (usually at least about  $10^7 \text{ M}^{-1}$ , preferably at least about  $10^8 \text{ M}^{-1}$ , more preferably at least about  $10^9 \text{ M}^{-1}$ ), and immunogenicity (e.g. ability to elicit MP53 specific antibody in a heterologous host such as a mouse, rat, goat or rabbit). For enzymes and receptors, binding may be assayed by, respectively, substrate and ligand processing.

The screening assay may measure a candidate agent's ability to specifically bind to or modulate activity of a MP53 polypeptide, a fusion protein thereof, or to cells or membranes bearing the polypeptide or fusion protein. The MP53 polypeptide can be full length or a fragment thereof that retains functional MP53 activity. The MP53 polypeptide may be fused to another polypeptide, such as a peptide tag for detection or anchoring, or to another tag. The MP53 polypeptide is preferably human MP53, or is an ortholog or derivative thereof as described above. In a preferred embodiment, the screening assay detects candidate agent-based modulation of MP53 interaction with a binding target, such as an endogenous or exogenous protein or other substrate that has MP53-specific binding activity, and can be used to assess normal MP53 gene function.

Suitable assay formats that may be adapted to screen for MP53 modulators are known in the art. Preferred screening assays are high throughput or ultra high throughput and thus provide automated, cost-effective means of screening compound libraries for lead compounds (Fernandes PB, Curr Opin Chem Biol (1998) 2:597-603; Sundberg SA, Curr Opin Biotechnol 2000, 11:47-53). In one preferred embodiment, screening assays uses fluorescence technologies, including fluorescence polarization, time-resolved fluorescence, and fluorescence resonance energy transfer. These systems offer means to monitor protein-protein or DNA-protein interactions in which the intensity of the signal emitted from dye-labeled molecules depends upon their interactions with partner molecules (e.g., Selvin PR, Nat Struct Biol (2000) 7:730-4; Fernandes PB, *supra*; Hertzberg RP and Pope AJ, Curr Opin Chem Biol (2000) 4:445-451).

A variety of suitable assay systems may be used to identify candidate MP53 and p53 pathway modulators (e.g. U.S. Pat. No. 6,165,992 (kinase assays); U.S. Pat. Nos. 5,550,019 and 6,133,437 (apoptosis assays); U.S. Pat. No. 6,020,135 (p53 modulation),

and U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434 (angiogenesis assays), among others). Specific preferred assays are described in more detail below.

Protein kinases, key signal transduction proteins that may be either membrane-associated or intracellular, catalyze the transfer of gamma phosphate from adenosine triphosphate (ATP) to a serine, threonine or tyrosine residue in a protein substrate. Radioassays, which monitor the transfer from [ $\gamma$ - $^{32}\text{P}$  or  $^{33}\text{P}$ ]ATP, are frequently used to assay kinase activity. For instance, a scintillation assay for p56 (lck) kinase activity monitors the transfer of the gamma phosphate from [ $\gamma$ - $^{33}\text{P}$ ] ATP to a biotinylated peptide substrate. The substrate is captured on a streptavidin coated bead that transmits the signal (Beveridge M *et al.*, J Biomol Screen (2000) 5:205-212). This assay uses the scintillation proximity assay (SPA), in which only radio-ligand bound to receptors tethered to the surface of an SPA bead are detected by the scintillant immobilized within it, allowing binding to be measured without separation of bound from free ligand. Other assays for protein kinase activity may use antibodies that specifically recognize phosphorylated substrates. For instance, the kinase receptor activation (KIRA) assay measures receptor tyrosine kinase activity by ligand stimulating the intact receptor in cultured cells, then capturing solubilized receptor with specific antibodies and quantifying phosphorylation via phosphotyrosine ELISA (Sadick MD, Dev Biol Stand (1999) 97:121-133). Another example of antibody based assays for protein kinase activity is TRF (time-resolved fluorometry). This method utilizes europium chelate-labeled anti-phosphotyrosine antibodies to detect phosphate transfer to a polymeric substrate coated onto microtiter plate wells. The amount of phosphorylation is then detected using time-resolved, dissociation-enhanced fluorescence (Braunwalder AF, et al., Anal Biochem 1996 Jul 1;238(2):159-64).

Protein phosphatases catalyze the removal of a gamma phosphate from a serine, threonine or tyrosine residue in a protein substrate. Since phosphatases act in opposition to kinases, appropriate assays measure the same parameters as kinase assays. In one example, the dephosphorylation of a fluorescently labeled peptide substrate allows trypsin cleavage of the substrate, which in turn renders the cleaved substrate significantly more fluorescent (Nishikata M *et al.*, Biochem J (1999) 343:35-391). In another example, fluorescence polarization (FP), a solution-based, homogeneous technique requiring no immobilization or separation of reaction components, is used to develop high throughput screening (HTS) assays for protein phosphatases. This assay uses direct binding of the phosphatase with the target, and increasing concentrations of target- phosphatase increase

the rate of dephosphorylation, leading to a change in polarization (Parker GJ et al., (2000) J Biomol Screen 5:77-88).

Endogenous protease inhibitors may inhibit protease activity. In an example of an assay developed for either proteases or protease inhibitors, a biotinylated substrate is  
5 coated on a titer plate and hydrolyzed with the protease; the unhydrolyzed substrate is quantified by reaction with alkaline phosphatase-streptavidin complex and detection of the reaction product. The activity of protease inhibitors correlates with the activity of the alkaline phosphatase indicator enzyme (Gan Z *et al.*, Anal Biochem 1999) 268:151-156).

Fatty acid desaturases catalyze the insertion of double bonds into saturated fatty  
10 acid molecules. In one application, radioassays for inhibitors of delta-5 and delta-6 fatty acid desaturase activity use thin layer chromatography to detect conversion of fatty acid substrates (Obukowicz et al., Biochem Pharmacol (1998) 55:1045-1058).

RNA folds into a myriad of tertiary structures that are responsible for its diverse functions in cells. In most instances, RNA is associated with RNA-binding proteins  
15 (RBPs) that protect, stabilize, package or transport RNA, mediate RNA interactions with other biomolecules or act catalytically on RNA. The structural information obtained for RNA alone and RNA-protein complexes has elucidated a variety of RNA tertiary structures and diverse modes for RNA-protein interaction. The specific interaction of proteins with highly structured RNAs makes it possible to target unique RNA motifs with  
20 small molecules, thus making RNA an interesting target for therapeutic intervention.

Assays for RNA binding or processing may be based on homogeneous scintillation proximity (Liu J, et al., Anal Biochem 2001 289:239-245), chemiluminescence (Mazumder A, Nucleic Acids Res 1998 26:1996-2000), gel shift (Stull RA, et al., Antisense Nucleic Acid Drug Dev 1996 6:221-228; U.S. Pat. No: 6004749).

Adapter proteins are involved in a wide range of signaling and other cellular  
25 processes and generally facilitate protein-protein or protein-nucleic acid interactions via certain conserved motifs, including PDZ, SH2, SH3, PH, TRAF, WD40, LIM, ankyrin repeat, KH and annexin domains, etc. Assays for adapter protein activity may measure protein binding at the conserved motifs. For instance, exemplary assays for SH2 domain-  
30 containing proteins have measured binding using fluorescently labeled peptide substrate and fluorescence polarization or laser-scanning techniques (Lynch BA et al., Anal Biochem 1999, 275:62-73; Zuck P et al., Proc Natl Acad Sci USA 1999, 96: 11122-11127). An alternative SH2 binding assay uses radiolabeled peptide. An assay for protein-protein interaction at the LIM domain has used fluorescently labeled LIM-

containing proteins (FHL2 and FHL3) and the fluorescence resonance energy transfer (FRET) technique (Li HY, J Cell Biochem 2001, 80:293-303).

Transporter proteins carry a range of substrates, including nutrients, ions, amino acids, and drugs, across cell membranes. Assays for modulators of transporters may use  
5 labeled substrates. For instance, exemplary high throughput screens to identify compounds that interact with different peptide and anion transporters both use fluorescently labeled substrates; the assay for peptide transport additionally uses multiscreen filtration plates (Blevitt JM et al., J Biomol Screen 1999, 4:87-91; Cihlar T and Ho ES, Anal Biochem 2000, 283:49-55).

10 Ion channels mediate essential physiological functions, including fluid secretion, electrolyte balance, bioenergetics, and membrane excitability. Assays for channel activity can incorporate ion-sensitive dyes or proteins or voltage-sensitive dyes or proteins, as reviewed in Gonzalez JE *et al.* (Drug Discovery Today (1999) 4:431-439). Alternative methods measure the displacement of known ligands, which may be radio-labeled or  
15 fluorescently labeled (*e.g.*, SchMid EL *et al.*, Anal Chem (1998) 70:1331-1338).

Transcription factors control gene transcription. Electrophoretic mobility shift assay (EMSA) or gel shift assay is one of the most powerful methods for studying protein-DNA interactions. High throughput gel shift assays for transcription factors may involve fluorescence (Cyano dye Cy5) labeled oligodeoxynucleotide duplexes as specific probes  
20 and an automatic DNA sequencer for analysis (Ruscher K, et al.; (2000) J Biotechnol 78:163-70). Alternatively high throughput methods involve colorimetric assays (Renard P, et al. (2001) Nucleic Acids Res 29(4):E21), or homogeneous fluorescence assays for the detection and quantification of sequence-specific DNA-binding proteins (Heyduk T, and Heyduk E (2001) Nat Biotechnol 20:171-6.)

25 Reductases are enzymes of oxidoreductase class that catalyze reactions in which metabolites are reduced. High throughput screening assays for reductases may involve scintillation (Fernandes PB. (1998) Curr Opin Chem Biol 2:597-603; Delaporte E et al. (2001) J Biomol Screen 6:225-231).

Assays for ATPase activity may be performed as described in Blackburn et al  
30 (Blackburn CL, et al., (1999) J Org Chem 64:5565-5570). The ATPase assay is performed using the EnzCheck ATPase kit (Molecular Probes). The assays are performed using an Ultraspec spectrophotometer (Pharmacia), and the progress of the reaction are monitored by absorbance increase at 360 nm. Microtubules (1.7 mM final), kinesin (0.11 mM final), inhibitor (or DMSO blank at 5% final), and the EnzCheck components (purine nucleotide

phosphorylase and MESG substrate) are premixed in the cuvette in a reaction buffer (40 mM PIPES pH 6.8, 5 mM paclitaxel, 1 mM EGTA, 5 mM MgCl<sub>2</sub>). The reaction is initiated by addition of MgATP (1 mM final).

High throughput assays based on photometric analysis of the activity of decarboxylase enzymes have been described (Breuer M et al (2002) Anal Bioanal Chem 374:1069-73).

High-throughput photometric assays for peroxidases have also been described (Smith AD et al (2001) Int J Vitam Nutr Res 71:87-92; Smith AD and Levander OA (2002) Methods Enzymol 347:113-21).

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**Apoptosis assays.** Assays for apoptosis may be performed by terminal deoxynucleotidyl transferase-mediated digoxigenin-11-dUTP nick end labeling (TUNEL) assay. The TUNEL assay is used to measure nuclear DNA fragmentation characteristic of apoptosis (Lazebnik *et al.*, 1994, Nature 371, 346), by following the incorporation of fluorescein-dUTP (Yonehara *et al.*, 1989, J. Exp. Med. 169, 1747). Apoptosis may further be assayed by acridine orange staining of tissue culture cells (Lucas, R., et al., 1998, Blood 15:4730-41). An apoptosis assay system may comprise a cell that expresses an MP53, and that optionally has defective p53 function (e.g. p53 is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the apoptosis assay system and changes in induction of apoptosis relative to controls where no test agent is added, identify candidate p53 modulating agents. In some embodiments of the invention, an apoptosis assay may be used as a secondary assay to test a candidate p53 modulating agents that is initially identified using a cell-free assay system. An apoptosis assay may also be used to test whether MP53 function plays a direct role in apoptosis. For example, an apoptosis assay may be performed on cells that over- or under-express MP53 relative to wild type cells. Differences in apoptotic response compared to wild type cells suggests that the MP53 plays a direct role in the apoptotic response. Apoptosis assays are described further in US Pat. No. 6,133,437.

**Cell proliferation and cell cycle assays.** Cell proliferation may be assayed via bromodeoxyuridine (BRDU) incorporation. This assay identifies a cell population undergoing DNA synthesis by incorporation of BRDU into newly-synthesized DNA. Newly-synthesized DNA may then be detected using an anti-BRDU antibody (Hoshino *et*

*al.*, 1986, *Int. J. Cancer* 38, 369; Campana *et al.*, 1988, *J. Immunol. Meth.* 107, 79), or by other means.

Cell proliferation is also assayed via phospho-histone H3 staining, which identifies a cell population undergoing mitosis by phosphorylation of histone H3. Phosphorylation of histone H3 at serine 10 is detected using an antibody specific to the phosphorylated form of the serine 10 residue of histone H3. (Chadlee, D.N. 1995, *J. Biol. Chem* 270:20098-105). Cell Proliferation may also be examined using [<sup>3</sup>H]-thymidine incorporation (Chen, J., 1996, *Oncogene* 13:1395-403; Jeoung, J., 1995, *J. Biol. Chem.* 270:18367-73). This assay allows for quantitative characterization of S-phase DNA syntheses. In this assay, cells synthesizing DNA will incorporate [<sup>3</sup>H]-thymidine into newly synthesized DNA. Incorporation can then be measured by standard techniques such as by counting of radioisotope in a scintillation counter (e.g., Beckman LS 3800 Liquid Scintillation Counter). Another proliferation assay uses the dye Alamar Blue (available from Biosource International), which fluoresces when reduced in living cells and provides an indirect measurement of cell number (Voytik-Harbin SL *et al.*, 1998, *In Vitro Cell Dev Biol Anim* 34:239-46).

Cell proliferation may also be assayed by colony formation in soft agar (Sambrook *et al.*, *Molecular Cloning*, Cold Spring Harbor (1989)). For example, cells transformed with MP53 are seeded in soft agar plates, and colonies are measured and counted after two weeks incubation.

Involvement of a gene in the cell cycle may be assayed by flow cytometry (Gray JW *et al.* (1986) *Int J Radiat Biol Relat Stud Phys Chem Med* 49:237-55). Cells transfected with an MP53 may be stained with propidium iodide and evaluated in a flow cytometer (available from Becton Dickinson), which indicates accumulation of cells in different stages of the cell cycle.

Accordingly, a cell proliferation or cell cycle assay system may comprise a cell that expresses an MP53, and that optionally has defective p53 function (e.g. p53 is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the assay system and changes in cell proliferation or cell cycle relative to controls where no test agent is added, identify candidate p53 modulating agents. In some embodiments of the invention, the cell proliferation or cell cycle assay may be used as a secondary assay to test a candidate p53 modulating agents that is initially identified using another assay system such as a cell-free assay system. A cell proliferation assay may also be used to test whether MP53 function plays a direct role in cell proliferation or cell cycle. For example,

a cell proliferation or cell cycle assay may be performed on cells that over- or under-express MP53 relative to wild type cells. Differences in proliferation or cell cycle compared to wild type cells suggests that the MP53 plays a direct role in cell proliferation or cell cycle.

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**Angiogenesis.** Angiogenesis may be assayed using various human endothelial cell systems, such as umbilical vein, coronary artery, or dermal cells. Suitable assays include Alamar Blue based assays (available from Biosource International) to measure proliferation; migration assays using fluorescent molecules, such as the use of Becton Dickinson Falcon HTS FluoroBlock cell culture inserts to measure migration of cells through membranes in presence or absence of angiogenesis enhancer or suppressors; and tubule formation assays based on the formation of tubular structures by endothelial cells on Matrigel® (Becton Dickinson). Accordingly, an angiogenesis assay system may comprise a cell that expresses an MP53, and that optionally has defective p53 function (e.g. p53 is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the angiogenesis assay system and changes in angiogenesis relative to controls where no test agent is added, identify candidate p53 modulating agents. In some embodiments of the invention, the angiogenesis assay may be used as a secondary assay to test a candidate p53 modulating agents that is initially identified using another assay system. An angiogenesis assay may also be used to test whether MP53 function plays a direct role in cell proliferation. For example, an angiogenesis assay may be performed on cells that over- or under-express MP53 relative to wild type cells. Differences in angiogenesis compared to wild type cells suggests that the MP53 plays a direct role in angiogenesis. U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434, among others, describe various angiogenesis assays.

**Hypoxic induction.** The alpha subunit of the transcription factor, hypoxia inducible factor-1 (HIF-1), is upregulated in tumor cells following exposure to hypoxia in vitro. Under hypoxic conditions, HIF-1 stimulates the expression of genes known to be important in tumour cell survival, such as those encoding glycolytic enzymes and VEGF. Induction of such genes by hypoxic conditions may be assayed by growing cells transfected with MP53 in hypoxic conditions (such as with 0.1% O<sub>2</sub>, 5% CO<sub>2</sub>, and balance N<sub>2</sub>, generated in a Napco 7001 incubator (Precision Scientific)) and normoxic conditions, followed by assessment of gene activity or expression by Taqman®. For



example, a hypoxic induction assay system may comprise a cell that expresses an MP53, and that optionally has defective p53 function (e.g. p53 is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the hypoxic induction assay system and changes in hypoxic response relative to controls where no test agent is added, identify candidate p53 modulating agents. In some embodiments of the invention, the hypoxic induction assay may be used as a secondary assay to test a candidate p53 modulating agents that is initially identified using another assay system. A hypoxic induction assay may also be used to test whether MP53 function plays a direct role in the hypoxic response. For example, a hypoxic induction assay may be performed on cells that over- or under-express MP53 relative to wild type cells. Differences in hypoxic response compared to wild type cells suggests that the MP53 plays a direct role in hypoxic induction.

**Cell adhesion.** Cell adhesion assays measure adhesion of cells to purified adhesion proteins, or adhesion of cells to each other, in presence or absence of candidate modulating agents. Cell-protein adhesion assays measure the ability of agents to modulate the adhesion of cells to purified proteins. For example, recombinant proteins are produced, diluted to 2.5g/mL in PBS, and used to coat the wells of a microtiter plate. The wells used for negative control are not coated. Coated wells are then washed, blocked with 1% BSA, and washed again. Compounds are diluted to 2× final test concentration and added to the blocked, coated wells. Cells are then added to the wells, and the unbound cells are washed off. Retained cells are labeled directly on the plate by adding a membrane-permeable fluorescent dye, such as calcein-AM, and the signal is quantified in a fluorescent microplate reader.

Cell-cell adhesion assays measure the ability of agents to modulate binding of cell adhesion proteins with their native ligands. These assays use cells that naturally or recombinantly express the adhesion protein of choice. In an exemplary assay, cells expressing the cell adhesion protein are plated in wells of a multiwell plate. Cells expressing the ligand are labeled with a membrane-permeable fluorescent dye, such as BCECF, and allowed to adhere to the monolayers in the presence of candidate agents. Unbound cells are washed off, and bound cells are detected using a fluorescence plate reader.

High-throughput cell adhesion assays have also been described. In one such assay, small molecule ligands and peptides are bound to the surface of microscope slides using a

microarray spotter, intact cells are then contacted with the slides, and unbound cells are washed off. In this assay, not only the binding specificity of the peptides and modulators against cell lines are determined, but also the functional cell signaling of attached cells using immunofluorescence techniques in situ on the microchip is measured (Falsey JR et al., Bioconjug Chem. 2001 May-Jun;12(3):346-53).

**Tubulogenesis.** Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which generally simulates the environment of the extracellular matrix. Exemplary substrates include Matrigel™ (Becton Dickinson), an extract of basement membrane proteins containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4° C and forms a solid gel at 37° C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF-alpha. Thus, in a further preferred embodiment, a tubulogenesis assay system comprises testing an MP53's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF-alpha, ephrin, etc.

**Cell Migration.** An invasion/migration assay (also called a migration assay) tests the ability of cells to overcome a physical barrier and to migrate towards pro-angiogenic signals. Migration assays are known in the art (e.g., Paik JH et al., 2001, J Biol Chem 276:11830-11837). In a typical experimental set-up, cultured endothelial cells are seeded onto a matrix-coated porous lamina, with pore sizes generally smaller than typical cell size. The matrix generally simulates the environment of the extracellular matrix, as described above. The lamina is typically a membrane, such as the transwell polycarbonate membrane (Corning Costar Corporation, Cambridge, MA), and is generally part of an

upper chamber that is in fluid contact with a lower chamber containing pro-angiogenic stimuli. Migration is generally assayed after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Migration is assessed as the number of cells that crossed the lamina, and may be detected by staining cells with hemotoxylin solution (VWR Scientific, South San Francisco, CA), or by any other method for determining cell number. In another exemplary set up, cells are fluorescently labeled and migration is detected using fluorescent readings, for instance using the Falcon HTS FluoroBlok (Becton Dickinson). While some migration is observed in the absence of stimulus, migration is greatly increased in response to pro-angiogenic factors. As described above, a preferred assay system for migration/invasion assays comprises testing an MP53's response to a variety of pro-angiogenic factors, including tumor angiogenic and inflammatory angiogenic agents, and culturing the cells in serum free medium.

**Sprouting assay.** A sprouting assay is a three-dimensional *in vitro* angiogenesis assay that uses a cell-number defined spheroid aggregation of endothelial cells ("spheroid"), embedded in a collagen gel-based matrix. The spheroid can serve as a starting point for the sprouting of capillary-like structures by invasion into the extracellular matrix (termed "cell sprouting") and the subsequent formation of complex anastomosing networks (Korff and Augustin, 1999, J Cell Sci 112:3249-58). In an exemplary experimental set-up, spheroids are prepared by pipetting 400 human umbilical vein endothelial cells into individual wells of a nonadhesive 96-well plates to allow overnight spheroidal aggregation (Korff and Augustin: J Cell Biol 143: 1341-52, 1998). Spheroids are harvested and seeded in 900 $\mu$ l of methocel-collagen solution and pipetted into individual wells of a 24 well plate to allow collagen gel polymerization. Test agents are added after 30 min by pipetting 100  $\mu$ l of 10-fold concentrated working dilution of the test substances on top of the gel. Plates are incubated at 37°C for 24h. Dishes are fixed at the end of the experimental incubation period by addition of paraformaldehyde. Sprouting intensity of endothelial cells can be quantitated by an automated image analysis system to determine the cumulative sprout length per spheroid.

#### ***Primary assays for antibody modulators***

For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MP53 protein. Methods for testing antibody affinity and specificity are well known in the art (Harlow and Lane, 1988, 1999,

*supra*). The enzyme-linked immunosorbant assay (ELISA) is a preferred method for detecting MP53-specific antibodies; others include FACS assays, radioimmunoassays, and fluorescent assays.

In some cases, screening assays described for small molecule modulators may also  
5 be used to test antibody modulators.

#### ***Primary assays for nucleic acid modulators***

For nucleic acid modulators, primary assays may test the ability of the nucleic acid modulator to inhibit or enhance MP53 gene expression, preferably mRNA expression. In  
10 general, expression analysis comprises comparing MP53 expression in like populations of cells (*e.g.*, two pools of cells that endogenously or recombinantly express MP53) in the presence and absence of the nucleic acid modulator. Methods for analyzing mRNA and protein expression are well known in the art. For instance, Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR (*e.g.*, using the TaqMan®, PE Applied  
15 Biosystems), or microarray analysis may be used to confirm that MP53 mRNA expression is reduced in cells treated with the nucleic acid modulator (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm DH and Guiseppi-Elie, A Curr Opin Biotechnol 2001, 12:41-47).  
20 Protein expression may also be monitored. Proteins are most commonly detected with specific antibodies or antisera directed against either the MP53 protein or specific peptides. A variety of means including Western blotting, ELISA, or in situ detection, are available (Harlow E and Lane D, 1988 and 1999, *supra*).

In some cases, screening assays described for small molecule modulators,  
25 particularly in assay systems that involve MP53 mRNA expression, may also be used to test nucleic acid modulators.

#### **Secondary Assays**

Secondary assays may be used to further assess the activity of MP53-modulating  
30 agent identified by any of the above methods to confirm that the modulating agent affects MP53 in a manner relevant to the p53 pathway. As used herein, MP53-modulating agents encompass candidate clinical compounds or other agents derived from previously identified modulating agent. Secondary assays can also be used to test the activity of a

modulating agent on a particular genetic or biochemical pathway or to test the specificity of the modulating agent's interaction with MP53.

Secondary assays generally compare like populations of cells or animals (*e.g.*, two pools of cells or animals that endogenously or recombinantly express MP53) in the presence and absence of the candidate modulator. In general, such assays test whether treatment of cells or animals with a candidate MP53–modulating agent results in changes in the p53 pathway in comparison to untreated (or mock- or placebo-treated) cells or animals. Certain assays use “sensitized genetic backgrounds”, which, as used herein, describe cells or animals engineered for altered expression of genes in the p53 or interacting pathways.

#### *Cell-based assays*

Cell based assays may use a variety of mammalian cell lines known to have defective p53 function (*e.g.* SAOS-2 osteoblasts, H1299 lung cancer cells, C33A and HT3 cervical cancer cells, HT-29 and DLD-1 colon cancer cells, among others, available from American Type Culture Collection (ATCC), Manassas, VA). Cell based assays may detect endogenous p53 pathway activity or may rely on recombinant expression of p53 pathway components. Any of the aforementioned assays may be used in this cell-based format. Candidate modulators are typically added to the cell media but may also be injected into cells or delivered by any other efficacious means.

#### *Animal Assays*

A variety of non-human animal models of normal or defective p53 pathway may be used to test candidate MP53 modulators. Models for defective p53 pathway typically use genetically modified animals that have been engineered to mis-express (*e.g.*, over-express or lack expression in) genes involved in the p53 pathway. Assays generally require systemic delivery of the candidate modulators, such as by oral administration, injection, etc.

In a preferred embodiment, p53 pathway activity is assessed by monitoring neovascularization and angiogenesis. Animal models with defective and normal p53 are used to test the candidate modulator's affect on MP53 in Matrigel® assays. Matrigel® is an extract of basement membrane proteins, and is composed primarily of laminin, collagen IV, and heparin sulfate proteoglycan. It is provided as a sterile liquid at 4°C, but rapidly forms a solid gel at 37°C. Liquid Matrigel® is mixed with various angiogenic agents,

such as bFGF and VEGF, or with human tumor cells which over-express the MP53. The mixture is then injected subcutaneously(SC) into female athymic nude mice (Taconic, Germantown, NY) to support an intense vascular response. Mice with Matrigel® pellets may be dosed via oral (PO), intraperitoneal (IP), or intravenous (IV) routes with the candidate modulator. Mice are euthanized 5 - 12 days post-injection, and the Matrigel® pellet is harvested for hemoglobin analysis (Sigma plasma hemoglobin kit). Hemoglobin content of the gel is found to correlate the degree of neovascularization in the gel.

In another preferred embodiment, the effect of the candidate modulator on MP53 is assessed via tumorigenicity assays. Tumor xenograft assays are known in the art (see, e.g., Ogawa K et al., 2000, *Oncogene* 19:6043-6052). Xenografts are typically implanted SC into female athymic mice, 6-7 week old, as single cell suspensions either from a pre-existing tumor or from *in vitro* culture. The tumors which express the MP53 endogenously are injected in the flank,  $1 \times 10^5$  to  $1 \times 10^7$  cells per mouse in a volume of 100  $\mu$ L using a 27gauge needle. Mice are then ear tagged and tumors are measured twice weekly. Candidate modulator treatment is initiated on the day the mean tumor weight reaches 100 mg. Candidate modulator is delivered IV, SC, IP, or PO by bolus administration. Depending upon the pharmacokinetics of each unique candidate modulator, dosing can be performed multiple times per day. The tumor weight is assessed by measuring perpendicular diameters with a caliper and calculated by multiplying the measurements of diameters in two dimensions. At the end of the experiment, the excised tumors maybe utilized for biomarker identification or further analyses. For immunohistochemistry staining, xenograft tumors are fixed in 4% paraformaldehyde, 0.1M phosphate, pH 7.2, for 6 hours at 4°C, immersed in 30% sucrose in PBS, and rapidly frozen in isopentane cooled with liquid nitrogen.

In another preferred embodiment, tumorigenicity is monitored using a hollow fiber assay, which is described in U.S. Pat No. US 5,698,413. Briefly, the method comprises implanting into a laboratory animal a biocompatible, semi-permeable encapsulation device containing target cells, treating the laboratory animal with a candidate modulating agent, and evaluating the target cells for reaction to the candidate modulator. Implanted cells are generally human cells from a pre-existing tumor or a tumor cell line. After an appropriate period of time, generally around six days, the implanted samples are harvested for evaluation of the candidate modulator. Tumorigenicity and modulator efficacy may be evaluated by assaying the quantity of viable cells present in the macrocapsule, which can be determined by tests known in the art, for example, MTT dye conversion assay, neutral

red dye uptake, trypan blue staining, viable cell counts, the number of colonies formed in soft agar, the capacity of the cells to recover and replicate in vitro, etc.

In another preferred embodiment, a tumorigenicity assay use a transgenic animal, usually a mouse, carrying a dominant oncogene or tumor suppressor gene knockout under the control of tissue specific regulatory sequences; these assays are generally referred to as transgenic tumor assays. In a preferred application, tumor development in the transgenic model is well characterized or is controlled. In an exemplary model, the "RIP1-Tag2" transgene, comprising the SV40 large T-antigen oncogene under control of the insulin gene regulatory regions is expressed in pancreatic beta cells and results in islet cell carcinomas (Hanahan D, 1985, Nature 315:115-122; Parangi S et al, 1996, Proc Natl Acad Sci USA 93: 2002-2007; Bergers G et al, 1999, Science 284:808-812). An "angiogenic switch," occurs at approximately five weeks, as normally quiescent capillaries in a subset of hyperproliferative islets become angiogenic. The RIP1-TAG2 mice die by age 14 weeks. Candidate modulators may be administered at a variety of stages, including just prior to the angiogenic switch (e.g., for a model of tumor prevention), during the growth of small tumors (e.g., for a model of intervention), or during the growth of large and/or invasive tumors (e.g., for a model of regression). Tumorigenicity and modulator efficacy can be evaluating life-span extension and/or tumor characteristics, including number of tumors, tumor size, tumor morphology, vessel density, apoptotic index, etc.

#### **Diagnostic and therapeutic uses**

Specific MP53-modulating agents are useful in a variety of diagnostic and therapeutic applications where disease or disease prognosis is related to defects in the p53 pathway, such as angiogenic, apoptotic, or cell proliferation disorders. Accordingly, the invention also provides methods for modulating the p53 pathway in a cell, preferably a cell pre-determined to have defective or impaired p53 function (e.g. due to overexpression, underexpression, or misexpression of p53, or due to gene mutations), comprising the step of administering an agent to the cell that specifically modulates MP53 activity. Preferably, the modulating agent produces a detectable phenotypic change in the cell indicating that the p53 function is restored. The phrase "function is restored", and equivalents, as used herein, means that the desired phenotype is achieved, or is brought closer to normal compared to untreated cells. For example, with restored p53 function, cell proliferation and/or progression through cell cycle may normalize, or be brought closer to normal relative to untreated cells. The invention also provides methods for

treating disorders or disease associated with impaired p53 function by administering a therapeutically effective amount of an MP53 -modulating agent that modulates the p53 pathway. The invention further provides methods for modulating MP53 function in a cell, preferably a cell pre-determined to have defective or impaired MP53 function, by  
5 administering an MP53 -modulating agent. Additionally, the invention provides a method for treating disorders or disease associated with impaired MP53 function by administering a therapeutically effective amount of an MP53 -modulating agent.

The discovery that MP53 is implicated in p53 pathway provides for a variety of methods that can be employed for the diagnostic and prognostic evaluation of diseases and  
10 disorders involving defects in the p53 pathway and for the identification of subjects having a predisposition to such diseases and disorders.

Various expression analysis methods can be used to diagnose whether MP53 expression occurs in a particular sample, including Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR, and microarray analysis. (*e.g.*, Current  
15 Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm and Guiseppi-Elie, Curr Opin Biotechnol 2001, 12:41-47). Tissues having a disease or disorder implicating defective p53 signaling that express an MP53, are identified as amenable to treatment with an MP53 modulating agent. In a  
20 preferred application, the p53 defective tissue overexpresses an MP53 relative to normal tissue. For example, a Northern blot analysis of mRNA from tumor and normal cell lines, or from tumor and matching normal tissue samples from the same patient, using full or partial MP53 cDNA sequences as probes, can determine whether particular tumors express or overexpress MP53. Alternatively, the TaqMan® is used for quantitative RT-PCR  
25 analysis of MP53 expression in cell lines, normal tissues and tumor samples (PE Applied Biosystems).

Various other diagnostic methods may be performed, for example, utilizing reagents such as the MP53 oligonucleotides, and antibodies directed against an MP53, as described above for: (1) the detection of the presence of MP53 gene mutations, or the  
30 detection of either over- or under-expression of MP53 mRNA relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of MP53 gene product relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the signal transduction pathway mediated by MP53.



Thus, in a specific embodiment, the invention is drawn to a method for diagnosing a disease or disorder in a patient that is associated with alterations in MP53 expression, the method comprising: a) obtaining a biological sample from the patient; b) contacting the sample with a probe for MP53 expression; c) comparing results from step (b) with a control; and d) determining whether step (c) indicates a likelihood of the disease or disorder. Preferably, the disease is cancer, most preferably a cancer as shown in TABLE 2. The probe may be either DNA or protein, including an antibody.

### EXAMPLES

The following experimental section and examples are offered by way of illustration and not by way of limitation.

#### I. Drosophila p53 screen

The Drosophila p53 gene was overexpressed specifically in the wing using the vestigial margin quadrant enhancer. Increasing quantities of Drosophila p53 (titrated using different strength transgenic inserts in 1 or 2 copies) caused deterioration of normal wing morphology from mild to strong, with phenotypes including disruption of pattern and polarity of wing hairs, shortening and thickening of wing veins, progressive crumpling of the wing and appearance of dark "death" inclusions in wing blade. In a screen designed to identify enhancers and suppressors of Drosophila p53, homozygous females carrying two copies of p53 were crossed to 5663 males carrying random insertions of a piggyBac transposon (Fraser M *et al.*, Virology (1985) 145:356-361). Progeny containing insertions were compared to non-insertion-bearing sibling progeny for enhancement or suppression of the p53 phenotypes. Sequence information surrounding the piggyBac insertion site was used to identify the modifier genes. Modifiers of the wing phenotype were identified as members of the p53 pathway. Modifiers (enhancers and suppressors of the wing phenotype). Orthologs of the modifiers are referred to herein as MP53.

#### II. Analysis of Table 1

BLAST analysis (Altschul et al., *supra*) was employed to identify orthologs of *Drosophila* modifiers. The columns "MP53 symbol", "MP53 name" and "MP53 name aliases" provide a symbol and the known name abbreviations for the Targets, where available, from Genbank. "MP53 RefSeq\_NA or GI\_NA", and "MP53 GI\_AA", provide the reference nucleotide and amino acid sequences for the MP53s as available from

National Center for Biology Information (NCBI), and Genbank, where available.

Nucleotide and amino acid SEQ ID Nos of the sequences used in the application are also provided.

Names and Protein sequences of *Drosophila* modifiers of p53 from screen

- 5 (Example I), are represented in the "Modifier genetic Name", "Modifier physical Name" and "Modifier GI\_AA" column by GI#, respectively.

Table 1

MP53 Symbol	MP53 name	MP53 name aliases	MP53 identifier NA RefSeq or GI#	NA SEQ ID NO	MP53 GI# AA	AA SEQ ID NO	Modifier genetic name	Modifier physical name	Modifier GI# AA
ANXA13	annexin A13	ANX13	XM_052383	1	4757754	57	AnnIX_(A nnexin IX)	CG5730	gi 17136266  ref NP_4766 04.1
ANXA4	annexin A4	ANX4	NM_001153	2	4502105	58	AnnIX_(A nnexin IX)	CG5730	gi 17136266  ref NP_4766 04.1
AXOT	axotrophin	DKFZP 586F11 22; axotrop hin	NM_022826	3	12383066	59	NA	CG14518	gi 7301726 g b AAF56839 .1
FLJ20085	hypothetical protein FLJ20085	-	XM_053238 .1	4	15308522	60	NA	CG7983	gi 7294806 g b AAF50140 .1
NYX	nyctalopin, alias: congenital stationary night blindness 4; Congenital stationary night blindness-1 (CSNB, complete)	dJ169I5 .2,CLR P, CSNB1, CSNB4	NM_022567	5	12314287	61	caps_(capr icious)	CG11282	gi 3885974 g b AAC7814 4.1
FLJ21302	hypothetical protein FLJ21302	-	NM_022901	6	12597641	62	caps_(capr icious)	CG11282	gi 3885974 g b AAC7814 4.1
GARP	glycoprotein A repetitions predominant	D11S83 3E	XM_006198	7	5031707	63	caps_(capr icious)	CG11282	gi 3885974 g b AAC7814 4.1
GP1BA	glycoprotein Ib (platelet), alpha polypeptide	CD42b	NM_000173	8	4504071	64	caps_(capr icious)	CG11282	gi 3885974 g b AAC7814 4.1
GP5	glycoprotein V (platelet)	CD42d	XM_002975	9	4758460	65	caps_(capr icious)	CG11282	gi 3885974 g b AAC7814 4.1
HT017	HT017 protein	-	XM_054557	10	10190722	66	caps_(capr icious)	CG11282	gi 3885974 g b AAC7814 4.1

KIAA0416	KIAA0416 protein	-	XM_003637	11	7662102	67	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
LY64	lymphocyte antigen 64 homolog, radioprotective 105kD (mouse)	RP105	XM_003933	12	13645378	68	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
LOC112684			XM_053144.1	13	15301270	69	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
ISLR			NM_005545.1	14	5031809	70	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
Unknown (protein for MGC:17113)			15489167	15	15489168	71	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
unnamed protein product CAC21785			12226531	16	12226532	72	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA1465			XM_027396.1	17	14752075	73	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
LOC115025			XM_028612.2	18	15294652	74	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
PAL			NM_015613.1	19	14149694	75	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA1246			XM_046690.2	20	15300859	76	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
MGC2656			NM_024509.1	21	13375646	77	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
unnamed protein product CAC49977			15132048	22	15132049	78	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA1910			XM_055514.1	23	16163269	79	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA0918			XM_054870.1	24	16188327	80	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
bG256022.1			5531259	25	6691962	81	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA0848			NM_014926.1	26	7662336	82	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
CASK			NM_003688.1	27	4502567	83	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1

APBA1		X11, X11A, MINT1, D9S411E, X11ALPHA	NM_001163.1	28	4502129	84	caps_(capricious)	CG11282	gi 3885974 gb AAC78144.1
LIN-7-C		LIN-7-C: LIN-7 protein 3	NM_018362.1	29	8922944	85	caps_(capricious)	CG11282	gi 3885974 gb AAC78144.1
TRIM3	tripartite motif-containing 3	RNF22	XM_044513	30	5453569	86	brat_(brain_tumor)	CG10719	gi 17136846 ref NP_476945.1
LBP-32	LBP protein 32	none	NM_014552	31	7657297	87	grh_grainyhead	CG2094	7302703
PTBP2	polypyrimidine tract binding protein 2	PTB, MIBP, nPTB, PTBLP, neural polypyrimidine tract binding protein	XM_042972	32	14722543	88	heph_hep haustus	CG2094	7302108
ROD1	ROD1 regulator of differentiation 1 (S. pombe)		NM_005156	33	4826984	89	heph_hep haustus	CG2094	7302108
PTBP1	polypyrimidine tract binding protein 1	PTB; PTB2; PTB3; PTB4; pPTB; HNRPI; PTB-1; HNRNP I	NM_002819	34	4506243	90	heph_hep haustus	CG2094	7302108
P4HA1	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide I	P4HA	NM_000917	35	4505565	91	none	SD05564p	15292529
P4HA2	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide II	prolyl 4-hydroxylase, alpha polypeptide, type 2; prolyl 4-	NM_004199	36	4758868	92	none	SD05564p	15292529

		hydroxy lase, alpha polypep tide, type II							
none	metastasis suppressor protein	none	6539605	37	6539606	93	none	CG9469	7302324
LOC92154	similar to Unknown (protein for IMAGE)	none	XM_043228	38	14779986	94	none	CG9469	7302324
LOC123676	similar to hypothetical protein, MNCb-1213 (H. sapiens)	none	XM_063793	39	17478005	95	none	CG5447	18488547
LOC51125	HSPC041 protein	none	NM_016099	40	7705821	96	none	CG5447	18488547
WFS1	Wolfram syndrome 1 (wolframin)	WFS, WFRS, DIDMO AD	NM_006005	41	5174749	97	none	mod_@tra nsmembra ne wolfram syndrome wolframin .transcript _3 translation	Exelixis internal
PPP1R16A	protein phosphatase 1, regulatory (inhibitor) subunit 16A	MYPT3 , MGC14 333; likely ortholog of mouse myosin phospha tase targetin g subunit 3	NM_032902	42	14249672	98	none	CG6896	7293882
PPP1R16B	protein phosphatase 1, regulatory (inhibitor) subunit 16B	TIMAP, ANKR D4, KIAA0 823	XM_028840	43	14770818	99	none	CG6896	7293882
CXorf9	chromosome X open reading frame 9	SLY, 753P9; likely ortholog of mouse SH3 gene SLY	NM_018990	44	9506363	100	none	mod_@ki aa0790.tra nscript_11 translation	Exelixis internal

LOC134963	similar to KIAA0790 protein (H. sapiens)	none	XM_044015	45	14751637	101	none	mod_@k aa0790.tra nscript_11 translation	Exelixis internal
SAMSN1	SAM domain, SH3 domain and nuclear localisation signals, 1	none	NM_022136	46	11545871	102	none	mod_@k aa0790.tra nscript_11 translation	Exelixis internal
MGC9564	similar to RIKEN cDNA 1110002C08 gene		NM_080669	47	18087847	103	none	CG15553	7302010
FKSG16	none	none	16416763	48	16416764	104	none	CG15553	7302010
BAG3	BCL2-associated athanogene 3	BIS, BAG-3, CAIR-1, DKFZp434E0610; Bcl-2-binding protein; docking protein CAIR-1; BCL2-binding athanogene 3; BAG-family molecular chaperone regulator-3	NM_004281	49	14043024	105	none	CG10745	16076828
BAG4	BCL2-associated athanogene 4	SODD, BAG-4; silencer of death domains; BAG-family molecular chaperone regulator-4	NM_004874	50	6631075	106	none	CG10745	16076828
FLJ22944	hypothetical protein FLJ22944		NM_025145	51	13376733	107	none	mod_@dk fzp434a20 17 flj11142.tr anscript_3	Exelixis internal

								translation	
FLJ11142	hypothetical protein FLJ11142		NM_018338	52	8922897	108	none	mod_@dk fzp434a20 17 flj11142.tr anscript_3 translation	Exelixis internal
BAZ1A	bromodomain adjacent to zinc finger domain, 1A	ACF1, WALp1, hACF1, WCRF180, DKFZP586E0518	NM_013448	53	7304919	109	Acfl_AT P-dependent chromatin assembly factor large subunit	CG1966	7302099
BAZ1B	bromodomain adjacent to zinc finger domain, 1B	WSTF, WBSCR9, WBSCR10; Williams-Beuren syndrome chromosome region	NM_023005	54	14670390	110	Acfl_AT P-dependent chromatin assembly factor large subunit	CG1966	7302099
FLJ21613	hypothetical protein FLJ21613 similar to rat corneal wound healing related protein	none	NM_021929	55	11345464	111	none	CG4065	7291750
KIAA0483	KIAA0483 protein	none	NM_015176	56	7022998	112	none	CG3428	7294925

### III. High-Throughput In Vitro Fluorescence Polarization Assay

Fluorescently-labeled MP53 peptide/substrate are added to each well of a 96-well microtiter plate, along with a test agent in a test buffer (10 mM HEPES, 10 mM NaCl, 6 mM magnesium chloride, pH 7.6). Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System (Dynatech Laboratories, Inc), relative to control values indicates the test compound is a candidate modifier of MP53 activity.

#### IV. High-Throughput In Vitro Binding Assay.

<sup>33</sup>P-labeled MP53 peptide is added in an assay buffer (100 mM KCl, 20 mM HEPES pH 7.6, 1 mM MgCl<sub>2</sub>, 1% glycerol, 0.5% NP-40, 50 mM beta-mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors) along with a test agent to the wells of a Neutralite-avidin coated assay plate and incubated at 25°C for 1 hour. Biotinylated substrate is then added to each well and incubated for 1 hour. Reactions are stopped by washing with PBS, and counted in a scintillation counter. Test agents that cause a difference in activity relative to control without test agent are identified as candidate p53 modulating agents.

#### V. Immunoprecipitations and Immunoblotting

For coprecipitation of transfected proteins,  $3 \times 10^6$  appropriate recombinant cells containing the MP53 proteins are plated on 10-cm dishes and transfected on the following day with expression constructs. The total amount of DNA is kept constant in each transfection by adding empty vector. After 24 h, cells are collected, washed once with phosphate-buffered saline and lysed for 20 min on ice in 1 ml of lysis buffer containing 50 mM Hepes, pH 7.9, 250 mM NaCl, 20 mM -glycerophosphate, 1 mM sodium orthovanadate, 5 mM p-nitrophenyl phosphate, 2 mM dithiothreitol, protease inhibitors (complete, Roche Molecular Biochemicals), and 1% Nonidet P-40. Cellular debris is removed by centrifugation twice at  $15,000 \times g$  for 15 min. The cell lysate is incubated with 25  $\mu$ l of M2 beads (Sigma) for 2 h at 4 °C with gentle rocking.

After extensive washing with lysis buffer, proteins bound to the beads are solubilized by boiling in SDS sample buffer, fractionated by SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membrane and blotted with the indicated antibodies. The reactive bands are visualized with horseradish peroxidase coupled to the appropriate secondary antibodies and the enhanced chemiluminescence (ECL) Western blotting detection system (Amersham Pharmacia Biotech).

#### VI. Kinase assay

A purified or partially purified MP53 is diluted in a suitable reaction buffer, e.g., 50 mM Hepes, pH 7.5, containing magnesium chloride or manganese chloride (1-20 mM) and a peptide or polypeptide substrate, such as myelin basic protein or casein (1-10  $\mu$ g/ml). The final concentration of the kinase is 1-20 nM. The enzyme reaction is conducted in microtiter plates to facilitate optimization of reaction conditions by



increasing assay throughput. A 96-well microtiter plate is employed using a final volume 30-100  $\mu$ l. The reaction is initiated by the addition of  $^{33}\text{P}$ -gamma-ATP (0.5  $\mu\text{Ci/ml}$ ) and incubated for 0.5 to 3 hours at room temperature. Negative controls are provided by the addition of EDTA, which chelates the divalent cation ( $\text{Mg}^{2+}$  or  $\text{Mn}^{2+}$ ) required for enzymatic activity. Following the incubation, the enzyme reaction is quenched using EDTA. Samples of the reaction are transferred to a 96-well glass fiber filter plate (MultiScreen, Millipore). The filters are subsequently washed with phosphate-buffered saline, dilute phosphoric acid (0.5%) or other suitable medium to remove excess radiolabeled ATP. Scintillation cocktail is added to the filter plate and the incorporated radioactivity is quantitated by scintillation counting (Wallac/Perkin Elmer). Activity is defined by the amount of radioactivity detected following subtraction of the negative control reaction value (EDTA quench).

## VII. Expression analysis

All cell lines used in the following experiments are NCI (National Cancer Institute) lines, and are available from ATCC (American Type Culture Collection, Manassas, VA 20110-2209). Normal and tumor tissues were obtained from Impath, UC Davis, Clontech, Stratagene, Ardaïs, Genome Collaborative, and Ambion.

TaqMan analysis was used to assess expression levels of the disclosed genes in various samples.

RNA was extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/ $\mu$ l. Single stranded cDNA was then synthesized by reverse transcribing the RNA samples using random hexamers and 500ng of total RNA per reaction, following protocol 4304965 of Applied Biosystems (Foster City, CA).

Primers for expression analysis using TaqMan assay (Applied Biosystems, Foster City, CA) were prepared according to the TaqMan protocols, and the following criteria: a) primer pairs were designed to span introns to eliminate genomic contamination, and b) each primer pair produced only one product. Expression analysis was performed using a 7900HT instrument.

Taqman reactions were carried out following manufacturer's protocols, in 25  $\mu$ l total volume for 96-well plates and 10  $\mu$ l total volume for 384-well plates, using 300nM primer and 250 nM probe, and approximately 25ng of cDNA. The standard curve for result analysis was prepared using a universal pool of human cDNA samples, which is a

mixture of cDNAs from a wide variety of tissues so that the chance that a target will be present in appreciable amounts is good. The raw data were normalized using 18S rRNA (universally expressed in all tissues and cells).

For each expression analysis, tumor tissue samples were compared with matched  
5 normal tissues from the same patient. A gene was considered overexpressed in a tumor when the level of expression of the gene was 2 fold or higher in the tumor compared with its matched normal sample. In cases where normal tissue was not available, a universal pool of cDNA samples was used instead. In these cases, a gene was considered  
10 overexpressed in a tumor sample when the difference of expression levels between a tumor sample and the average of all normal samples from the same tissue type was greater than 2 times the standard deviation of all normal samples (i.e.,  $\text{Tumor} - \text{average}(\text{all normal samples}) > 2 \times \text{STDEV}(\text{all normal samples})$  ).

Results are shown in Table 2. Number of pairs of tumor samples and matched normal tissue from the same patient are shown for each tumor type. Percentage of the  
15 samples with at least two-fold overexpression for each tumor type is provided. ND indicates not done. A modulator identified by an assay described herein can be further validated for therapeutic effect by administration to a tumor in which the gene is overexpressed. A decrease in tumor growth confirms therapeutic utility of the modulator. Prior to treating a patient with the modulator, the likelihood that the patient will respond to  
20 treatment can be diagnosed by obtaining a tumor sample from the patient, and assaying for expression of the gene targeted by the modulator. The expression data for the gene(s) can also be used as a diagnostic marker for disease progression. The assay can be performed by expression analysis as described above, by antibody directed to the gene target, or by  
25 any other available detection method.

Table 2

SEQ ID NO:	Breast	# of Pairs	Colon	# of Pairs	Head and Neck	# of Pairs	Kidney	# of Pairs	Lung	# of Pairs	Ovary	# of Pairs	Prostate	# of Pairs	Skin	# of Pairs	Uterus	# of Pairs
48	5%	21	6%	33	12%	8	12%	24	5%	21	9%	11	17%	12	0%	3	11%	19
52	5%	21	6%	33	12%	8	8%	24	0%	21	9%	11	17%	12	0%	3	21%	19
4	5%	21	6%	33	12%	8	8%	24	0%	21	9%	11	17%	12	0%	3	21%	19
6	33%	6	17%	30	ND	ND	ND	ND	8%	12	20%	5	ND	ND	ND	ND	ND	ND
55	33%	6	17%	30	ND	ND	ND	ND	8%	12	20%	5	ND	ND	ND	ND	ND	ND
51	33%	6	17%	30	ND	ND	ND	ND	8%	12	20%	5	ND	ND	ND	ND	ND	ND
7	0%	12	50%	30	ND	ND	ND	ND	0%	14	14%	7	ND	ND	ND	ND	ND	ND
8	33%	12	10%	29	ND	ND	ND	ND	21%	14	29%	7	ND	ND	ND	ND	ND	ND
9	8%	12	33%	30	ND	ND	ND	ND	7%	14	14%	7	ND	ND	ND	ND	ND	ND
10	100%	1	0%	8	ND	ND	ND	ND	0%	2	ND	ND	ND	ND	ND	ND	ND	ND
11	0%	12	7%	28	ND	ND	ND	ND	7%	14	14%	7	ND	ND	ND	ND	ND	ND
56	0%	12	7%	28	ND	ND	ND	ND	7%	14	14%	7	ND	ND	ND	ND	ND	ND
31	5%	21	6%	33	25%	8	12%	24	5%	21	0%	11	8%	12	33%	3	5%	19
40	17%	18	22%	23	25%	8	20%	20	6%	18	10%	10	0%	8	33%	3	20%	15
38	17%	18	22%	23	25%	8	20%	20	6%	18	10%	10	0%	8	33%	3	20%	15
12	25%	12	17%	30	ND	ND	ND	ND	21%	14	0%	6	ND	ND	ND	ND	ND	ND
47	14%	21	18%	33	25%	8	29%	24	5%	21	10%	10	8%	12	67%	3	0%	19
5	8%	12	14%	14	ND	ND	ND	ND	18%	11	14%	7	ND	ND	ND	ND	ND	ND
42	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
43	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
34	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
32	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
33	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
30	33%	21	67%	33	25%	8	83%	24	10%	21	36%	11	17%	12	33%	3	58%	19

## WHAT IS CLAIMED IS:

1. A method of identifying a candidate p53 pathway modulating agent, said method comprising the steps of:
  - 5 (a) providing an assay system comprising a MP53 polypeptide or nucleic acid;
  - (b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and
  - (c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as
  - 10 a candidate p53 pathway modulating agent.
2. The method of Claim 1 wherein the assay system comprises cultured cells that express the MP53 polypeptide.
- 15 3. The method of Claim 2 wherein the cultured cells additionally have defective p53 function.
4. The method of Claim 1 wherein the assay system includes a screening assay comprising a MP53 polypeptide, and the candidate test agent is a small molecule
- 20 modulator.
5. The method of Claim 4 wherein the assay is a binding assay.
6. The method of Claim 1 wherein the assay system is selected from the group consisting
- 25 of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay system, and a hypoxic induction assay system.
7. The method of Claim 1 wherein the assay system includes a binding assay comprising a MP53 polypeptide and the candidate test agent is an antibody.
- 30 8. The method of Claim 1 wherein the assay system includes an expression assay comprising a MP53 nucleic acid and the candidate test agent is a nucleic acid modulator.
9. The method of Claim 8 wherein the nucleic acid modulator is an antisense oligomer.

10. The method of Claim 8 wherein the nucleic acid modulator is a PMO.
11. The method of Claim 1 additionally comprising:
- 5 (d) administering the candidate p53 pathway modulating agent identified in (c) to a model system comprising cells defective in p53 function and, detecting a phenotypic change in the model system that indicates that the p53 function is restored.
12. The method of Claim 11 wherein the model system is a mouse model with defective p53 function.
- 10 13. A method for modulating a p53 pathway of a cell comprising contacting a cell defective in p53 function with a candidate modulator that specifically binds to a MP53 polypeptide, whereby p53 function is restored.
- 15 14. The method of Claim 13 wherein the candidate modulator is administered to a vertebrate animal predetermined to have a disease or disorder resulting from a defect in p53 function.
- 20 15. The method of Claim 13 wherein the candidate modulator is selected from the group consisting of an antibody and a small molecule.
16. The method of Claim 1, comprising the additional steps of:
- (e) providing a secondary assay system comprising cultured cells or a non-human animal expressing MP53 ,
- 25 (f) contacting the secondary assay system with the test agent of (b) or an agent derived therefrom under conditions whereby, but for the presence of the test agent or agent derived therefrom, the system provides a reference activity; and
- (g) detecting an agent-biased activity of the second assay system,
- 30 wherein a difference between the agent-biased activity and the reference activity of the second assay system confirms the test agent or agent derived therefrom as a candidate p53 pathway modulating agent,
- and wherein the second assay detects an agent-biased change in the p53 pathway.

17. The method of Claim 16 wherein the secondary assay system comprises cultured cells.
18. The method of Claim 16 wherein the secondary assay system comprises a non-human  
5 animal.
19. The method of Claim 18 wherein the non-human animal mis-expresses a p53 pathway gene.
- 10 20. A method of modulating p53 pathway in a mammalian cell comprising contacting the cell with an agent that specifically binds a MP53 polypeptide or nucleic acid.
21. The method of Claim 20 wherein the agent is administered to a mammalian animal predetermined to have a pathology associated with the p53 pathway.  
15
22. The method of Claim 20 wherein the agent is a small molecule modulator, a nucleic acid modulator, or an antibody.
23. A method for diagnosing a disease in a patient comprising:  
20 (a) obtaining a biological sample from the patient;  
(b) contacting the sample with a probe for MP53 expression;  
(c) comparing results from step (b) with a control;  
(d) determining whether step (c) indicates a likelihood of disease.
- 25 24. The method of claim 23 wherein said disease is cancer.
25. The method according to claim 24, wherein said cancer is a cancer as shown in Table 2 as having >25% expression level.

30

## SEQUENCE LISTING

&lt;110&gt; EXELIXIS, INC.

&lt;120&gt; MP53s AS MODIFIERS OF THE p53 PATHWAY AND METHODS OF USE

&lt;130&gt; EX03-018C-PC

&lt;150&gt; US 60/361,196

&lt;151&gt; 2002-03-01

&lt;160&gt; 112

&lt;170&gt; PatentIn version 3.2

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 <212> DNA  
 <213> Homo sapiens

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<210> 56
<211> 2923
<212> DNA
<213> Homo sapiens

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<210> 57  
 <211> 316  
 <212> PRT  
 <213> Homo sapiens

<400> 57

Met Gly Asn Arg His Ala Lys Ala Ser Ser Pro Gln Gly Phe Asp Val  
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Asp Arg Asp Ala Lys Lys Leu Asn Lys Ala Cys Lys Gly Met Gly Thr  
 20 25 30

Asn Glu Ala Ala Ile Ile Glu Ile Leu Ser Gly Arg Thr Ser Asp Glu  
 35 40 45

Arg Gln Gln Ile Lys Gln Lys Tyr Lys Ala Thr Tyr Gly Lys Glu Leu  
 50 55 60

Glu Glu Val Leu Lys Ser Glu Leu Ser Gly Asn Phe Glu Lys Thr Ala  
 65 70 75 80

Leu Ala Leu Leu Asp Arg Pro Ser Glu Tyr Ala Ala Arg Gln Leu Gln  
 85 90 95

Lys Ala Met Lys Gly Leu Gly Thr Asp Glu Ser Val Leu Ile Glu Phe  
 100 105 110

Leu Cys Thr Arg Thr Asn Lys Glu Ile Ile Ala Ile Lys Glu Ala Tyr  
 115 120 125

Gln Arg Leu Phe Asp Arg Ser Leu Glu Ser Asp Val Lys Gly Asp Thr  
 130 135 140

Ser Gly Asn Leu Lys Lys Ile Leu Val Ser Leu Leu Gln Ala Asn Arg  
 145 150 155 160

Asn Glu Gly Asp Asp Val Asp Lys Asp Leu Ala Gly Gln Asp Ala Lys  
 165 170 175

Asp Leu Tyr Asp Ala Gly Glu Gly Arg Trp Gly Thr Asp Glu Leu Ala  
 180 185 190

Phe Asn Glu Val Leu Ala Lys Arg Ser Tyr Lys Gln Leu Arg Ala Thr  
 195 200 205

Phe Gln Ala Tyr Gln Ile Leu Ile Gly Lys Asp Ile Glu Glu Ala Ile  
 210 215 220

Glu Glu Glu Thr Ser Gly Asp Leu Gln Lys Ala Tyr Leu Thr Leu Val  
 225 230 235 240

Arg Cys Ala Gln Asp Cys Glu Asp Tyr Phe Ala Glu Arg Leu Tyr Lys  
 245 250 255

Ser Met Lys Gly Ala Gly Thr Asp Glu Glu Thr Leu Ile Arg Ile Val  
 260 265 270

Val Thr Arg Ala Glu Val Asp Leu Gln Gly Ile Lys Ala Lys Phe Gln  
 275 280 285

Glu Lys Tyr Gln Lys Ser Leu Ser Asp Met Val Arg Ser Asp Thr Ser  
 290 295 300

Gly Asp Phe Arg Lys Leu Leu Val Ala Leu Leu His  
 305 310 315

<210> 58  
 <211> 321  
 <212> PRT  
 <213> Homo sapiens

<400> 58

Met Ala Met Ala Thr Lys Gly Gly Thr Val Lys Ala Ala Ser Gly Phe  
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Asn Ala Met Glu Asp Ala Gln Thr Leu Arg Lys Ala Met Lys Gly Leu  
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Gly Thr Asp Glu Asp Ala Ile Ile Ser Val Leu Ala Tyr Arg Asn Thr  
 35 40 45

Ala Gln Arg Gln Glu Ile Arg Thr Ala Tyr Lys Ser Thr Ile Gly Arg  
 50 55 60

Asp Leu Ile Asp Asp Leu Lys Ser Glu Leu Ser Gly Asn Phe Glu Gln  
 65 70 75 80

Val Ile Val Gly Met Met Thr Pro Thr Val Leu Tyr Asp Val Gln Glu  
 85 90 95

Leu Arg Arg Ala Met Lys Gly Ala Gly Thr Asp Glu Gly Cys Leu Ile  
 100 105 110  
 Glu Ile Leu Ala Ser Arg Thr Pro Glu Glu Ile Arg Arg Ile Ser Gln  
 115 120 125  
 Thr Tyr Gln Gln Gln Tyr Gly Arg Ser Leu Glu Asp Asp Ile Arg Ser  
 130 135 140  
 Asp Thr Ser Phe Met Phe Gln Arg Val Leu Val Ser Leu Ser Ala Gly  
 145 150 155 160  
 Gly Arg Asp Glu Gly Asn Tyr Leu Asp Asp Ala Leu Val Arg Gln Asp  
 165 170 175  
 Ala Gln Asp Leu Tyr Glu Ala Gly Glu Lys Lys Trp Gly Thr Asp Glu  
 180 185 190  
 Val Lys Phe Leu Thr Val Leu Cys Ser Arg Asn Arg Asn His Leu Leu  
 195 200 205  
 His Val Phe Asp Glu Tyr Lys Arg Ile Ser Gln Lys Asp Ile Glu Gln  
 210 215 220  
 Ser Ile Lys Ser Glu Thr Ser Gly Ser Phe Glu Asp Ala Leu Leu Ala  
 225 230 235 240  
 Ile Val Lys Cys Met Arg Asn Lys Ser Ala Tyr Phe Ala Glu Lys Leu  
 245 250 255  
 Tyr Lys Ser Met Lys Gly Leu Gly Thr Asp Asp Asn Thr Leu Ile Arg  
 260 265 270  
 Val Met Val Ser Arg Ala Glu Ile Asp Met Leu Asp Ile Arg Ala His  
 275 280 285  
 Phe Lys Arg Leu Tyr Gly Lys Ser Leu Tyr Ser Phe Ile Lys Gly Asp  
 290 295 300  
 Thr Ser Gly Asp Tyr Arg Lys Val Leu Leu Val Leu Cys Gly Gly Asp  
 305 310 315 320  
 Asp

&lt;210&gt; 59

&lt;211&gt; 704

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 59

Met Glu Ser Lys Pro Ser Arg Ile Pro Arg Arg Ile Ser Val Gln Pro  
 1 5 10 15

Ser Ser Ser Leu Ser Ala Arg Met Met Ser Gly Ser Arg Gly Ser Ser  
 20 25 30

Leu Asn Asp Thr Tyr His Ser Arg Asp Ser Ser Phe Arg Leu Asp Ser  
 35 40 45

Glu Tyr Gln Ser Thr Ser Ala Ser Ala Ser Ala Ser Pro Phe Gln Ser  
 50 55 60

Ala Trp Tyr Ser Glu Ser Glu Ile Thr Gln Gly Ala Arg Ser Arg Ser  
 65 70 75 80

Gln Asn Gln Gln Arg Asp His Asp Ser Lys Arg Pro Lys Leu Ser Cys  
 85 90 95

Thr Asn Cys Thr Thr Ser Ala Gly Arg Asn Val Gly Asn Gly Leu Asn  
 100 105 110

Thr Leu Ser Asp Ser Ser Trp Arg His Ser Gln Val Pro Arg Ser Ser  
 115 120 125

Ser Met Val Leu Gly Ser Phe Gly Thr Asp Leu Met Arg Glu Arg Arg  
 130 135 140

Asp Leu Glu Arg Arg Thr Asp Ser Ser Ile Ser Asn Leu Met Asp Tyr  
 145 150 155 160

Ser His Arg Ser Gly Asp Phe Thr Thr Ser Ser Tyr Val Gln Asp Arg  
 165 170 175

Val Pro Ser Tyr Ser Gln Gly Ala Arg Pro Lys Glu Asn Ser Met Ser  
 180 185 190

Thr Leu Gln Leu Asn Thr Ser Ser Thr Asn His Gln Leu Pro Ser Glu  
 195 200 205

His Gln Thr Ile Leu Ser Ser Arg Asp Ser Arg Asn Ser Leu Arg Ser  
 210 215 220

Asn Phe Ser Ser Arg Glu Ser Glu Ser Ser Arg Ser Asn Thr Gln Pro  
 225 230 235 240

Gly Phe Ser Tyr Ser Ser Ser Arg Asp Glu Ala Pro Ile Ile Ser Asn  
 245 250 255

Ser Glu Arg Val Val Ser Ser Gln Arg Pro Phe Gln Glu Ser Ser Asp  
 260 265 270

Asn Glu Gly Arg Arg Thr Thr Arg Arg Leu Leu Ser Arg Ile Ala Ser  
 275 280 285

Ser Met Ser Ser Thr Phe Phe Ser Arg Arg Ser Ser Gln Asp Ser Leu  
 290 295 300

Asn Thr Arg Ser Leu Asn Ser Glu Asn Ser Tyr Val Ser Pro Arg Ile  
 305 310 315 320

Leu Thr Ala Ser Gln Ser Arg Ser Asn Val Pro Ser Ala Ser Glu Val  
 325 330 335

Pro Asp Asn Arg Ala Ser Glu Ala Ser Gln Gly Phe Arg Phe Leu Arg  
 340 345 350

Arg Arg Trp Gly Leu Ser Ser Leu Ser His Asn His Ser Ser Glu Ser  
 355 360 365

Asp Ser Glu Asn Phe Asn Gln Glu Ser Glu Gly Arg Asn Thr Gly Pro  
 370 375 380

Trp Leu Ser Ser Ser Leu Arg Asn Arg Cys Thr Pro Leu Phe Ser Arg  
 385 390 395 400

Arg Arg Arg Glu Gly Arg Asp Glu Ser Ser Arg Ile Pro Thr Ser Asp  
 405 410 415

Thr Ser Ser Arg Ser His Ile Phe Arg Arg Glu Ser Asn Glu Val Val  
 420 425 430

His Leu Glu Ala Gln Asn Asp Pro Leu Gly Ala Ala Ala Asn Arg Pro  
 435 440 445

Gln Ala Ser Ala Ala Ser Ser Ser Ala Thr Thr Gly Gly Ser Thr Ser  
 450 455 460

Asp Ser Ala Gln Gly Gly Arg Asn Thr Gly Ile Ser Gly Ile Leu Pro  
 465 470 475 480

Gly Ser Leu Phe Arg Phe Ala Val Pro Pro Ala Leu Gly Ser Asn Leu  
                             485                            490                            495

Thr Asp Asn Val Met Ile Thr Val Asp Ile Ile Pro Ser Gly Trp Asn  
                             500                            505                            510

Ser Ala Asp Gly Lys Ser Asp Lys Thr Lys Ser Ala Pro Ser Arg Asp  
                             515                            520                            525

Pro Glu Arg Leu Gln Lys Ile Lys Glu Ser Leu Leu Leu Glu Asp Ser  
                             530                            535                            540

Glu Glu Glu Glu Gly Asp Leu Cys Arg Ile Cys Gln Met Ala Ala Ala  
                             545                            550                            555                            560

Ser Ser Ser Asn Leu Leu Ile Glu Pro Cys Lys Cys Thr Gly Ser Leu  
                             565                            570                            575

Gln Tyr Val His Gln Asp Cys Met Lys Lys Trp Leu Gln Ala Lys Ile  
                             580                            585                            590

Asn Ser Gly Ser Ser Leu Glu Ala Val Thr Thr Cys Glu Leu Cys Lys  
                             595                            600                            605

Glu Lys Leu Glu Leu Asn Leu Glu Asp Phe Asp Ile His Glu Leu His  
                             610                            615                            620

Arg Ala His Ala Asn Glu Gln Ala Glu Tyr Glu Phe Ile Ser Ser Gly  
                             625                            630                            635                            640

Leu Tyr Leu Val Val Leu Leu His Leu Cys Glu Gln Ser Phe Ser Asp  
                             645                            650                            655

Met Met Gly Asn Thr Asn Glu Pro Ser Thr Arg Val Arg Phe Ile Asn  
                             660                            665                            670

Leu Ala Arg Thr Leu Gln Ala His Met Glu Asp Leu Glu Thr Ser Glu  
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Asp Asp Ser Glu Glu Asp Gly Asp His Asn Arg Thr Phe Asp Ile Ala  
                             690                            695                            700

<210> 60  
 <211> 490  
 <212> PRT  
 <213> Homo sapiens



&lt;400&gt; 60

Met Ile Lys Gln Leu Lys Glu Glu Leu Arg Leu Glu Glu Ala Lys Leu  
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Val Leu Leu Lys Lys Leu Arg Gln Ser Gln Ile Gln Lys Glu Ala Thr  
 20 25 30

Ala Gln Lys Pro Thr Gly Ser Val Gly Ser Thr Val Thr Thr Pro Pro  
 35 40 45

Pro Leu Val Arg Gly Thr Gln Asn Ile Pro Ala Gly Lys Pro Ser Leu  
 50 55 60

Gln Thr Ser Ser Ala Arg Met Pro Gly Ser Val Ile Pro Pro Pro Leu  
 65 70 75 80

Val Arg Gly Gly Gln Gln Ala Ser Ser Lys Leu Gly Pro Gln Ala Ser  
 85 90 95

Ser Gln Val Val Met Pro Pro Leu Val Arg Gly Ala Gln Gln Ile His  
 100 105 110

Ser Ile Arg Gln His Ser Ser Thr Gly Pro Pro Pro Leu Leu Leu Ala  
 115 120 125

Pro Arg Ala Ser Val Pro Ser Val Gln Ile Gln Gly Gln Arg Ile Ile  
 130 135 140

Gln Gln Gly Leu Ile Arg Val Ala Asn Val Pro Asn Thr Ser Leu Leu  
 145 150 155 160

Val Asn Ile Pro Gln Pro Thr Pro Ala Ser Leu Lys Gly Thr Thr Ala  
 165 170 175

Thr Ser Ala Gln Ala Asn Ser Thr Pro Thr Ser Val Ala Ser Val Val  
 180 185 190

Thr Ser Ala Glu Ser Pro Ala Ser Arg Gln Ala Ala Ala Lys Leu Ala  
 195 200 205

Leu Arg Lys Gln Leu Glu Lys Thr Leu Leu Glu Ile Pro Pro Pro Lys  
 210 215 220

Pro Pro Ala Pro Glu Met Asn Phe Leu Pro Ser Ala Ala Asn Asn Glu  
 225 230 235 240

Phe Ile Tyr Leu Val Gly Leu Glu Glu Val Val Gln Asn Leu Leu Glu  
245 250 255

Thr Gln Gly Arg Met Ser Ala Ala Thr Val Leu Ser Arg Glu Pro Tyr  
260 265 270

Met Cys Ala Gln Cys Lys Thr Asp Phe Thr Cys Arg Trp Arg Glu Glu  
275 280 285

Lys Ser Gly Ala Ile Met Cys Glu Asn Cys Met Thr Thr Asn Gln Lys  
290 295 300

Lys Ala Leu Lys Val Glu His Thr Ser Arg Leu Lys Ala Ala Phe Val  
305 310 315 320

Lys Ala Leu Gln Gln Glu Gln Glu Ile Glu Gln Arg Leu Leu Gln Gln  
325 330 335

Gly Thr Ala Pro Ala Gln Ala Lys Ala Glu Pro Thr Ala Ala Pro His  
340 345 350

Pro Val Leu Lys Gln Val Ile Lys Pro Arg Arg Lys Leu Ala Phe Arg  
355 360 365

Ser Gly Glu Ala Arg Asp Trp Ser Asn Gly Ala Val Leu Gln Ala Ser  
370 375 380

Ser Gln Leu Ser Arg Gly Ser Ala Thr Thr Pro Arg Gly Val Leu His  
385 390 395 400

Thr Phe Ser Pro Ser Pro Lys Leu Gln Asn Ser Ala Ser Ala Thr Ala  
405 410 415

Leu Val Ser Arg Thr Gly Arg His Ser Glu Arg Thr Val Ser Ala Gly  
420 425 430

Lys Gly Ser Ala Thr Ser Asn Trp Lys Lys Thr Pro Leu Ser Thr Gly  
435 440 445

Gly Thr Leu Ala Phe Val Ser Pro Ser Leu Ala Val His Lys Ser Ser  
450 455 460

Ser Ala Val Asp Arg Gln Arg Glu Tyr Leu Leu Asp Met Ile Pro Pro  
465 470 475 480

Arg Ser Ile Pro Gln Ser Ala Thr Trp Lys

485

490

<210> 61  
 <211> 495  
 <212> PRT  
 <213> Homo sapiens

<400> 61

Met Ser Ser Glu Ile Pro Gln Gly Leu Gln Thr Thr Asn Pro Gln Gly  
 1 5 10 15

His Ile Leu Val Phe Pro Asp Gln Thr Glu Ala Val Val Leu Gly Leu  
 20 25 30

Pro Ser Ala Trp Ala Val Gly Ala Cys Ala Arg Ala Cys Pro Ala Ala  
 35 40 45

Cys Ala Cys Ser Thr Val Glu Arg Gly Cys Ser Val Arg Cys Asp Arg  
 50 55 60

Ala Gly Leu Leu Arg Val Pro Ala Glu Leu Pro Cys Glu Ala Val Ser  
 65 70 75 80

Ile Asp Leu Asp Arg Asn Gly Leu Arg Phe Leu Gly Glu Arg Ala Phe  
 85 90 95

Gly Thr Leu Pro Ser Leu Arg Arg Leu Ser Leu Arg His Asn Asn Leu  
 100 105 110

Ser Phe Ile Thr Pro Gly Ala Phe Lys Gly Leu Pro Arg Leu Ala Glu  
 115 120 125

Leu Arg Leu Ala His Asn Gly Asp Leu Arg Tyr Leu His Ala Arg Thr  
 130 135 140

Phe Ala Ala Leu Ser Arg Leu Arg Arg Leu Asp Leu Ala Ala Cys Arg  
 145 150 155 160

Leu Phe Ser Val Pro Glu Arg Leu Leu Ala Glu Leu Pro Ala Leu Arg  
 165 170 175

Glu Leu Ala Ala Phe Asp Asn Leu Phe Arg Arg Val Pro Gly Ala Leu  
 180 185 190

Arg Gly Leu Ala Asn Leu Thr His Ala His Leu Glu Arg Gly Arg Ile  
 195 200 205

Glu Ala Val Ala Ser Ser Ser Leu Gln Gly Leu Arg Arg Leu Arg Ser  
 210 215 220

Leu Ser Leu Gln Ala Asn Arg Val Arg Ala Val His Ala Gly Ala Phe  
 225 230 235 240

Gly Asp Cys Gly Val Leu Glu His Leu Leu Leu Asn Asp Asn Leu Leu  
 245 250 255

Ala Glu Leu Pro Ala Asp Ala Phe Arg Gly Leu Arg Arg Leu Arg Thr  
 260 265 270

Leu Asn Leu Gly Gly Asn Ala Leu Asp Arg Val Ala Arg Ala Trp Phe  
 275 280 285

Ala Asp Leu Ala Glu Leu Glu Leu Leu Tyr Leu Asp Arg Asn Ser Ile  
 290 295 300

Ala Phe Val Glu Glu Gly Ala Phe Gln Asn Leu Ser Gly Leu Leu Ala  
 305 310 315 320

Leu His Leu Asn Gly Asn Arg Leu Thr Val Leu Ala Trp Val Ala Phe  
 325 330 335

Gln Pro Gly Phe Phe Leu Gly Arg Leu Phe Leu Phe Arg Asn Pro Trp  
 340 345 350

Cys Cys Asp Cys Arg Leu Glu Trp Leu Arg Asp Trp Met Glu Gly Ser  
 355 360 365

Gly Arg Val Thr Asp Val Pro Cys Ala Ser Pro Gly Ser Val Ala Gly  
 370 375 380

Leu Asp Leu Ser Gln Val Thr Phe Gly Arg Ser Ser Asp Gly Leu Cys  
 385 390 395 400

Val Asp Pro Glu Glu Leu Asn Leu Thr Thr Ser Ser Pro Gly Pro Ser  
 405 410 415

Pro Glu Pro Ala Ala Thr Thr Val Ser Arg Phe Ser Ser Leu Leu Ser  
 420 425 430

Lys Leu Leu Ala Pro Arg Val Pro Val Glu Glu Ala Ala Asn Thr Thr  
 435 440 445

Gly Gly Leu Ala Asn Ala Ser Leu Ser Asp Ser Leu Ser Ser Arg Gly  
 450 455 460

Val Gly Gly Ala Gly Arg Gln Pro Trp Phe Leu Leu Ala Ser Cys Leu  
 465 470 475 480

Leu Pro Ser Val Ala Gln His Val Val Phe Gly Leu Gln Met Asp  
 485 490 495

<210> 62  
 <211> 370  
 <212> PRT  
 <213> Homo sapiens

<400> 62

Met Lys Val Thr Gly Ile Thr Ile Leu Phe Trp Pro Leu Ser Met Ile  
 1 5 10 15

Leu Leu Ser Asp Lys Ile Gln Ser Ser Lys Arg Glu Val Gln Cys Asn  
 20 25 30

Phe Thr Glu Lys Asn Tyr Thr Leu Ile Pro Ala Asp Ile Lys Lys Asp  
 35 40 45

Val Thr Ile Leu Asp Leu Ser Tyr Asn Gln Ile Thr Leu Asn Gly Thr  
 50 55 60

Asp Thr Arg Val Leu Gln Thr Tyr Phe Leu Leu Thr Glu Leu Tyr Leu  
 65 70 75 80

Ile Glu Asn Lys Val Thr Ile Leu His Asn Asn Gly Phe Gly Asn Leu  
 85 90 95

Ser Ser Leu Glu Ile Leu Asn Ile Cys Arg Asn Ser Ile Tyr Val Ile  
 100 105 110

Gln Gln Gly Ala Phe Leu Gly Leu Asn Lys Leu Lys Gln Leu Tyr Leu  
 115 120 125

Cys Gln Asn Lys Ile Glu Gln Leu Asn Ala Asp Val Phe Val Pro Leu  
 130 135 140

Arg Ser Leu Lys Leu Leu Asn Leu Gln Gly Asn Leu Ile Ser Tyr Leu  
 145 150 155 160

Asp Val Pro Pro Leu Phe His Leu Glu Leu Ile Thr Leu Tyr Gly Asn  
 165 170 175

Leu Trp Asn Cys Ser Cys Ser Leu Phe Asn Leu Gln Asn Trp Leu Asn

180	185	190																
Thr Ser Asn Val Thr Leu Glu Asn Glu Asn Ile Thr Met Cys Ser Tyr																		
195	200	205																
Pro Asn Ser Leu Gln Ser Tyr Asn Ile Lys Thr Val Pro His Lys Ala																		
210	215	220																
Glu Cys His Ser Lys Phe Pro Ser Ser Val Thr Glu Asp Leu Tyr Ile																		
225	230	235																
His Phe Gln Pro Ile Ser Asn Ser Ile Phe Asn Ser Ser Ser Asn Asn																		
245	250	255																
Leu Thr Arg Asn Ser Glu His Glu Pro Leu Gly Lys Ser Trp Ala Phe																		
260	265	270																
Leu Val Gly Val Val Val Thr Val Leu Thr Thr Ser Leu Leu Ile Phe																		
275	280	285																
Ile Ala Ile Lys Cys Pro Ile Trp Tyr Asn Ile Leu Leu Ser Tyr Asn																		
290	295	300																
His His Arg Leu Glu Glu His Glu Ala Glu Thr Tyr Glu Asp Gly Phe																		
305	310	315																
Thr Gly Asn Pro Ser Ser Leu Ser Gln Ile Pro Glu Thr Asn Ser Glu																		
325	330	335																
Glu Thr Thr Val Ile Phe Glu Gln Leu His Ser Phe Val Val Asp Asp																		
340	345	350																
Asp Gly Phe Ile Glu Asp Lys Tyr Ile Asp Ile His Glu Leu Cys Glu																		
355	360	365																
Glu Asn																		
370																		
<210>	63																	
<211>	662																	
<212>	PRT																	
<213>	Homo sapiens																	
<400>	63																	
Met Arg Pro Gln Ile Leu Leu Leu Leu Ala Leu Leu Thr Leu Gly Leu																		
1	5	10	15															

Ala Ala Gln His Gln Asp Lys Val Pro Cys Lys Met Val Asp Lys Lys  
                   20                                  25                                  30

Val Ser Cys Gln Val Leu Gly Leu Leu Gln Val Pro Ser Val Leu Pro  
           35                                  40                                  45

Pro Asp Thr Glu Thr Leu Asp Leu Ser Gly Asn Gln Leu Arg Ser Ile  
       50                                  55                                  60

Leu Ala Ser Pro Leu Gly Phe Tyr Thr Ala Leu Arg His Leu Asp Leu  
   65                                  70                                  75                                  80

Ser Thr Asn Glu Ile Ser Phe Leu Gln Pro Gly Ala Phe Gln Ala Leu  
                   85                                  90                                  95

Thr His Leu Glu His Leu Ser Leu Ala His Asn Arg Leu Ala Met Ala  
                   100                                  105                                  110

Thr Ala Leu Ser Ala Gly Gly Leu Gly Pro Leu Pro Arg Val Thr Ser  
       115                                  120                                  125

Leu Asp Leu Ser Gly Asn Ser Leu Tyr Ser Gly Leu Leu Glu Arg Leu  
       130                                  135                                  140

Leu Gly Glu Ala Pro Ser Leu His Thr Leu Ser Leu Ala Glu Asn Ser  
   145                                  150                                  155                                  160

Leu Thr Arg Leu Thr Arg His Thr Phe Arg Asp Met Pro Ala Leu Glu  
                   165                                  170                                  175

Gln Leu Asp Leu His Ser Asn Val Leu Met Asp Ile Glu Asp Gly Ala  
                   180                                  185                                  190

Phe Glu Gly Leu Pro Arg Leu Thr His Leu Asn Leu Ser Arg Asn Ser  
           195                                  200                                  205

Leu Thr Cys Ile Ser Asp Phe Ser Leu Gln Gln Leu Arg Val Leu Asp  
       210                                  215                                  220

Leu Ser Cys Asn Ser Ile Glu Ala Phe Gln Thr Ala Ser Gln Pro Gln  
   225                                  230                                  235                                  240

Ala Glu Phe Gln Leu Thr Trp Leu Asp Leu Arg Glu Asn Lys Leu Leu  
                   245                                  250                                  255

His Phe Pro Asp Leu Ala Ala Leu Pro Arg Leu Ile Tyr Leu Asn Leu  
           260                                  265                                  270

Ser Asn Asn Leu Ile Arg Leu Pro Thr Gly Pro Pro Gln Asp Ser Lys  
 275 280 285

Gly Ile His Ala Pro Ser Glu Gly Trp Ser Ala Leu Pro Leu Ser Ala  
 290 295 300

Pro Ser Gly Asn Ala Ser Gly Arg Pro Leu Ser Gln Leu Leu Asn Leu  
 305 310 315 320

Asp Leu Ser Tyr Asn Glu Ile Glu Leu Ile Pro Asp Ser Phe Leu Glu  
 325 330 335

His Leu Thr Ser Leu Cys Phe Leu Asn Leu Ser Arg Asn Cys Leu Arg  
 340 345 350

Thr Phe Glu Ala Arg Arg Leu Gly Ser Leu Pro Cys Leu Met Leu Leu  
 355 360 365

Asp Leu Ser His Asn Ala Leu Glu Thr Leu Glu Leu Gly Ala Arg Ala  
 370 375 380

Leu Gly Ser Leu Arg Thr Leu Leu Leu Gln Gly Asn Ala Leu Arg Asp  
 385 390 395 400

Leu Pro Pro Tyr Thr Phe Ala Asn Leu Ala Ser Leu Gln Arg Leu Asn  
 405 410 415

Leu Gln Gly Asn Arg Val Ser Pro Cys Gly Gly Pro Asp Glu Pro Gly  
 420 425 430

Pro Ser Gly Cys Val Ala Phe Ser Gly Ile Thr Ser Leu Arg Ser Leu  
 435 440 445

Ser Leu Val Asp Asn Glu Ile Glu Leu Leu Arg Ala Gly Ala Phe Leu  
 450 455 460

His Thr Pro Leu Thr Glu Leu Asp Leu Ser Ser Asn Pro Gly Leu Glu  
 465 470 475 480

Val Ala Thr Gly Ala Leu Gly Gly Leu Glu Ala Ser Leu Glu Val Leu  
 485 490 495

Ala Leu Gln Gly Asn Gly Leu Met Val Leu Gln Val Asp Leu Pro Cys  
 500 505 510



Phe Ile Cys Leu Lys Arg Leu Asn Leu Ala Glu Asn Arg Leu Ser His  
515 520 525

Leu Pro Ala Trp Thr Gln Ala Val Ser Leu Glu Val Leu Asp Leu Arg  
530 535 540

Asn Asn Ser Phe Ser Leu Leu Pro Gly Ser Ala Met Gly Gly Leu Glu  
545 550 555 560

Thr Ser Leu Arg Arg Leu Tyr Leu Gln Gly Asn Pro Leu Ser Cys Cys  
565 570 575

Gly Asn Gly Trp Leu Ala Ala Gln Leu His Gln Gly Arg Val Asp Val  
580 585 590

Asp Ala Thr Gln Asp Leu Ile Cys Arg Phe Ser Ser Gln Glu Glu Val  
595 600 605

Ser Leu Ser His Val Arg Pro Glu Asp Cys Glu Lys Gly Gly Leu Lys  
610 615 620

Asn Ile Asn Leu Ile Ile Ile Leu Thr Phe Ile Leu Val Ser Ala Ile  
625 630 635 640

Leu Leu Thr Thr Leu Ala Ala Cys Cys Cys Val Arg Arg Gln Lys Phe  
645 650 655

Asn Gln Gln Tyr Lys Ala  
660

<210> 64  
<211> 626  
<212> PRT  
<213> Homo sapiens

<400> 64

Met Pro Leu Leu Leu Leu Leu Leu Leu Leu Pro Ser Pro Leu His Pro  
1 5 10 15

His Pro Ile Cys Glu Val Ser Lys Val Ala Ser His Leu Glu Val Asn  
20 25 30

Cys Asp Lys Arg Asn Leu Thr Ala Leu Pro Pro Asp Leu Pro Lys Asp  
35 40 45

Thr Thr Ile Leu His Leu Ser Glu Asn Leu Leu Tyr Thr Phe Ser Leu  
50 55 60

Ala Thr Leu Met Pro Tyr Thr Arg Leu Thr Gln Leu Asn Leu Asp Arg  
65 70 75 80

Cys Glu Leu Thr Lys Leu Gln Val Asp Gly Thr Leu Pro Val Leu Gly  
85 90 95

Thr Leu Asp Leu Ser His Asn Gln Leu Gln Ser Leu Pro Leu Leu Gly  
100 105 110

Gln Thr Leu Pro Ala Leu Thr Val Leu Asp Val Ser Phe Asn Arg Leu  
115 120 125

Thr Ser Leu Pro Leu Gly Ala Leu Arg Gly Leu Gly Glu Leu Gln Glu  
130 135 140

Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu  
145 150 155 160

Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu  
165 170 175

Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr  
180 185 190

Leu Leu Leu Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe  
195 200 205

Gly Ser His Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu  
210 215 220

Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala  
225 230 235 240

Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Lys Ala Met Thr  
245 250 255

Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val  
260 265 270

Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp  
275 280 285

Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys  
290 295 300

Val Arg Ala Thr Arg Thr Val Val Lys Phe Pro Thr Lys Ala His Thr

305                      310                      315                      320  
 Thr Pro Trp Gly Leu Phe Tyr Ser Trp Ser Thr Ala Ser Leu Asp Ser  
                                  325                      330                      335  
 Gln Met Pro Ser Ser Leu His Pro Thr Gln Glu Ser Thr Lys Glu Gln  
                                  340                      345                      350  
 Thr Thr Phe Pro Pro Arg Trp Thr Pro Asn Phe Thr Leu His Met Glu  
                                  355                      360                      365  
 Ser Ile Thr Phe Ser Lys Thr Pro Lys Ser Thr Thr Glu Pro Thr Pro  
                                  370                      375                      380  
 Ser Pro Thr Thr Ser Glu Pro Val Pro Glu Pro Ala Pro Asn Met Thr  
                                  385                      390                      395                      400  
 Thr Leu Glu Pro Thr Pro Ser Pro Thr Thr Pro Glu Pro Thr Ser Glu  
                                  405                      410                      415  
 Pro Ala Pro Ser Pro Thr Thr Pro Glu Pro Thr Pro Ile Pro Thr Ile  
                                  420                      425                      430  
 Ala Thr Ser Pro Thr Ile Leu Val Ser Ala Thr Ser Leu Ile Thr Pro  
                                  435                      440                      445  
 Lys Ser Thr Phe Leu Thr Thr Thr Lys Pro Val Ser Leu Leu Glu Ser  
                                  450                      455                      460  
 Thr Lys Lys Thr Ile Pro Glu Leu Asp Gln Pro Pro Lys Leu Arg Gly  
                                  465                      470                      475                      480  
 Val Leu Gln Gly His Leu Glu Ser Ser Arg Asn Asp Pro Phe Leu His  
                                  485                      490                      495  
 Pro Asp Phe Cys Cys Leu Leu Pro Leu Gly Phe Tyr Val Leu Gly Leu  
                                  500                      505                      510  
 Phe Trp Leu Leu Phe Ala Ser Val Val Leu Ile Leu Leu Leu Ser Trp  
                                  515                      520                      525  
 Val Gly His Val Lys Pro Gln Ala Leu Asp Ser Gly Gln Gly Ala Ala  
                                  530                      535                      540  
 Leu Thr Thr Ala Thr Gln Thr Thr His Leu Glu Leu Gln Arg Gly Arg  
                                  545                      550                      555                      560

Gln Val Thr Val Pro Arg Ala Trp Leu Leu Phe Leu Arg Gly Ser Leu  
                           565                          570                          575

Pro Thr Phe Arg Ser Ser Leu Phe Leu Trp Val Arg Pro Asn Gly Arg  
                           580                          585                          590

Val Gly Pro Leu Val Ala Gly Arg Arg Pro Ser Ala Leu Ser Gln Gly  
                           595                          600                          605

Arg Gly Gln Asp Leu Leu Ser Thr Val Ser Ile Arg Tyr Ser Gly His  
                           610                          615                          620

Ser Leu  
 625

<210> 65  
 <211> 560  
 <212> PRT  
 <213> Homo sapiens  
 <400> 65

Met Leu Arg Gly Thr Leu Leu Cys Ala Val Leu Gly Leu Leu Arg Ala  
 1                          5                          10                          15

Gln Pro Phe Pro Cys Pro Pro Ala Cys Lys Cys Val Phe Arg Asp Ala  
                           20                          25                          30

Ala Gln Cys Ser Gly Gly Asp Val Ala Arg Ile Ser Ala Leu Gly Leu  
                           35                          40                          45

Pro Thr Asn Leu Thr His Ile Leu Leu Phe Gly Met Gly Arg Gly Val  
                           50                          55                          60

Leu Gln Ser Gln Ser Phe Ser Gly Met Thr Val Leu Gln Arg Leu Met  
 65                          70                          75                          80

Ile Ser Asp Ser His Ile Ser Ala Val Ala Pro Gly Thr Phe Ser Asp  
                           85                          90                          95

Leu Ile Lys Leu Lys Thr Leu Arg Leu Ser Arg Asn Lys Ile Thr His  
                           100                          105                          110

Leu Pro Gly Ala Leu Leu Asp Lys Met Val Leu Leu Glu Gln Leu Phe  
                           115                          120                          125

Leu Asp His Asn Ala Leu Arg Gly Ile Asp Gln Asn Met Phe Gln Lys  
                           130                          135                          140

Leu Val Asn Leu Gln Glu Leu Ala Leu Asn Gln Asn Gln Leu Asp Phe  
 145 150 155 160

Leu Pro Ala Ser Leu Phe Thr Asn Leu Glu Asn Leu Lys Leu Leu Asp  
 165 170 175

Leu Ser Gly Asn Asn Leu Thr His Leu Pro Lys Gly Leu Leu Gly Ala  
 180 185 190

Gln Ala Lys Leu Glu Arg Leu Leu Leu His Ser Asn Arg Leu Val Ser  
 195 200 205

Leu Asp Ser Gly Leu Leu Asn Ser Leu Gly Ala Leu Thr Glu Leu Gln  
 210 215 220

Phe His Arg Asn His Ile Arg Ser Ile Ala Pro Gly Ala Phe Asp Arg  
 225 230 235 240

Leu Pro Asn Leu Ser Ser Leu Thr Leu Ser Arg Asn His Leu Ala Phe  
 245 250 255

Leu Pro Ser Ala Leu Phe Leu His Ser His Asn Leu Thr Leu Leu Thr  
 260 265 270

Leu Phe Glu Asn Pro Leu Ala Glu Leu Pro Gly Val Leu Phe Gly Glu  
 275 280 285

Met Gly Gly Leu Gln Glu Leu Trp Leu Asn Arg Thr Gln Leu Arg Thr  
 290 295 300

Leu Pro Ala Ala Ala Phe Arg Asn Leu Ser Arg Leu Arg Tyr Leu Gly  
 305 310 315 320

Val Thr Leu Ser Pro Arg Leu Ser Ala Leu Pro Gln Gly Ala Phe Gln  
 325 330 335

Gly Leu Gly Glu Leu Gln Val Leu Ala Leu His Ser Asn Gly Leu Thr  
 340 345 350

Ala Leu Pro Asp Gly Leu Leu Arg Gly Leu Gly Lys Leu Arg Gln Val  
 355 360 365

Ser Leu Arg Arg Asn Arg Leu Arg Ala Leu Pro Arg Ala Leu Phe Arg  
 370 375 380

Asn Leu Ser Ser Leu Glu Ser Val Gln Leu Asp His Asn Gln Leu Glu  
385 390 395 400

Thr Leu Pro Gly Asp Val Phe Gly Ala Leu Pro Arg Leu Thr Glu Val  
405 410 415

Leu Leu Gly His Asn Ser Trp Arg Cys Asp Cys Gly Leu Gly Pro Phe  
420 425 430

Leu Gly Trp Leu Arg Gln His Leu Gly Leu Val Gly Gly Glu Glu Pro  
435 440 445

Pro Arg Cys Ala Gly Pro Gly Ala His Ala Gly Leu Pro Leu Trp Ala  
450 455 460

Leu Pro Gly Gly Asp Ala Glu Cys Pro Gly Pro Arg Gly Pro Pro Pro  
465 470 475 480

Arg Pro Ala Ala Asp Ser Ser Ser Glu Ala Pro Val His Pro Ala Leu  
485 490 495

Ala Pro Asn Ser Ser Glu Pro Trp Val Trp Ala Gln Pro Val Thr Thr  
500 505 510

Gly Lys Gly Gln Asp His Ser Pro Phe Trp Gly Phe Tyr Phe Leu Leu  
515 520 525

Leu Ala Val Gln Ala Met Ile Thr Val Ile Ile Val Phe Ala Met Ile  
530 535 540

Lys Ile Gly Gln Leu Phe Arg Lys Leu Ile Arg Glu Arg Ala Leu Gly  
545 550 555 560

<210> 66

<211> 345

<212> PRT

<213> Homo sapiens

<400> 66

Met Lys Gly Glu Leu Leu Leu Phe Ser Ser Val Ile Val Leu Leu Gln  
1 5 10 15

Val Val Cys Ser Cys Pro Asp Lys Cys Tyr Cys Gln Ser Ser Thr Asn  
20 25 30

Phe Val Asp Cys Ser Gln Gln Gly Leu Ala Glu Ile Pro Ser His Leu  
35 40 45

Pro Pro Gln Thr Arg Thr Leu His Leu Gln Asp Asn Gln Ile His His  
 50 55 60

Leu Pro Ala Phe Ala Phe Arg Ser Val Pro Trp Leu Met Thr Leu Asn  
 65 70 75 80

Leu Ser Asn Asn Ser Leu Ser Asn Leu Ala Pro Gly Ala Phe His Gly  
 85 90 95

Leu Gln His Leu Gln Val Leu Asn Leu Thr Gln Asn Ser Leu Leu Ser  
 100 105 110

Leu Glu Ser Arg Leu Phe His Ser Leu Pro Gln Leu Arg Glu Leu Asp  
 115 120 125

Leu Ser Ser Asn Asn Ile Ser His Leu Pro Thr Ser Leu Gly Glu Thr  
 130 135 140

Trp Glu Asn Leu Thr Ile Leu Ala Val Gln Gln Asn Gln Leu Gln Gln  
 145 150 155 160

Leu Asp Arg Ala Leu Leu Glu Ser Met Pro Ser Val Arg Leu Leu Leu  
 165 170 175

Leu Lys Asp Asn Leu Trp Lys Cys Asn Cys His Leu Leu Gly Leu Lys  
 180 185 190

Leu Trp Leu Glu Lys Phe Val Tyr Lys Gly Gly Leu Thr Asp Gly Ile  
 195 200 205

Ile Cys Glu Ser Pro Asp Thr Trp Lys Gly Lys Asp Leu Leu Arg Ile  
 210 215 220

Pro His Glu Leu Tyr Gln Pro Cys Pro Leu Pro Ala Pro Asp Pro Val  
 225 230 235 240

Ser Ser Gln Ala Gln Trp Pro Gly Ser Ala His Gly Val Val Leu Arg  
 245 250 255

Pro Pro Glu Asn His Asn Ala Gly Glu Arg Glu Leu Leu Glu Cys Glu  
 260 265 270

Leu Lys Pro Lys Pro Arg Pro Ala Asn Leu Arg His Ala Ile Ala Thr  
 275 280 285

Val Ile Ile Thr Gly Val Val Cys Gly Ile Val Cys Leu Met Met Leu

290                                      295                                      300  
 Ala Ala Ala Ile Tyr Gly Cys Thr Tyr Ala Ala Ile Thr Ala Gln Tyr  
 305                                      310                                      315                                      320  
 His Gly Gly Pro Leu Ala Gln Thr Asn Asp Pro Gly Lys Val Glu Glu  
                                     325                                      330                                      335  
 Lys Glu Arg Phe Asp Ser Ser Pro Ala  
                                     340                                      345  
  
 <210> 67  
 <211> 516  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 67  
 Met Gly Leu His Phe Lys Trp Pro Leu Gly Ala Pro Met Leu Ala Ala  
 1                                      5                                      10                                      15  
 Ile Tyr Ala Met Ser Met Val Leu Lys Met Leu Pro Ala Leu Gly Met  
                                     20                                      25                                      30  
 Ala Cys Pro Pro Lys Cys Arg Cys Glu Lys Leu Leu Phe Tyr Cys Asp  
                                     35                                      40                                      45  
 Ser Gln Gly Phe His Ser Val Pro Asn Ala Thr Asp Lys Gly Ser Leu  
                                     50                                      55                                      60  
 Gly Leu Ser Leu Arg His Asn His Ile Thr Glu Leu Glu Arg Asp Gln  
 65                                      70                                      75                                      80  
 Phe Ala Ser Phe Ser Gln Leu Thr Trp Leu His Leu Asp His Asn Gln  
                                     85                                      90                                      95  
 Ile Ser Thr Val Lys Glu Asp Ala Phe Gln Gly Leu Tyr Lys Leu Lys  
                                     100                                      105                                      110  
 Glu Leu Ile Leu Ser Ser Asn Lys Ile Phe Tyr Leu Pro Asn Thr Thr  
                                     115                                      120                                      125  
 Phe Thr Gln Leu Ile Asn Leu Gln Asn Leu Asp Leu Ser Phe Asn Gln  
                                     130                                      135                                      140  
 Leu Ser Ser Leu His Pro Glu Leu Phe Tyr Gly Leu Arg Lys Leu Gln  
 145                                      150                                      155                                      160



Thr Leu His Leu Arg Ser Asn Ser Leu Arg Thr Ile Pro Val Arg Leu  
 165 170 175

Phe Trp Asp Cys Arg Ser Leu Glu Phe Leu Asp Leu Ser Thr Asn Arg  
 180 185 190

Leu Arg Ser Leu Ala Arg Asn Gly Phe Ala Gly Leu Ile Lys Leu Arg  
 195 200 205

Glu Leu His Leu Glu His Asn Gln Leu Thr Lys Ile Asn Phe Ala His  
 210 215 220

Phe Leu Arg Leu Ser Ser Leu His Thr Leu Phe Leu Gln Trp Asn Lys  
 225 230 235 240

Ile Ser Asn Leu Thr Cys Gly Met Glu Trp Thr Trp Gly Thr Leu Glu  
 245 250 255

Lys Leu Asp Leu Thr Gly Asn Glu Ile Lys Ala Ile Asp Leu Thr Val  
 260 265 270

Phe Glu Thr Met Pro Asn Leu Lys Ile Leu Leu Met Asp Asn Asn Lys  
 275 280 285

Leu Asn Ser Leu Asp Ser Lys Ile Leu Asn Ser Leu Arg Ser Leu Thr  
 290 295 300

Thr Val Gly Leu Ser Gly Asn Leu Trp Glu Cys Ser Ala Arg Ile Cys  
 305 310 315 320

Ala Leu Ala Ser Trp Leu Gly Ser Phe Gln Gly Arg Trp Glu His Ser  
 325 330 335

Ile Leu Cys His Ser Pro Asp His Thr Gln Gly Glu Asp Ile Leu Asp  
 340 345 350

Ala Val His Gly Phe Gln Leu Cys Trp Asn Leu Ser Thr Thr Val Thr  
 355 360 365

Val Met Ala Thr Thr Tyr Arg Asp Pro Thr Thr Glu Tyr Thr Lys Arg  
 370 375 380

Ile Ser Ser Ser Ser Tyr His Val Gly Asp Lys Glu Ile Pro Thr Thr  
 385 390 395 400

Ala Gly Ile Ala Val Thr Thr Glu Glu His Phe Pro Glu Pro Asp Asn  
 405 410 415

Ala Ile Phe Thr Gln Arg Val Ile Thr Gly Thr Met Ala Leu Leu Phe  
 420 425 430

Ser Phe Phe Phe Ile Ile Phe Ile Val Phe Ile Ser Arg Lys Cys Cys  
 435 440 445

Pro Pro Thr Leu Arg Arg Ile Arg Gln Cys Ser Met Val Gln Asn His  
 450 455 460

Arg Gln Leu Arg Ser Gln Thr Arg Leu His Met Ser Asn Met Ser Asp  
 465 470 475 480

Gln Gly Pro Tyr Asn Glu Tyr Glu Pro Thr His Glu Gly Pro Phe Ile  
 485 490 495

Ile Ile Asn Gly Tyr Gly Gln Cys Lys Cys Gln Gln Leu Pro Tyr Lys  
 500 505 510

Glu Cys Glu Val  
 515

<210> 68  
 <211> 661  
 <212> PRT  
 <213> Homo sapiens

<400> 68

Met Ala Phe Asp Val Ser Cys Phe Phe Trp Val Val Leu Phe Ser Ala  
 1 5 10 15

Gly Cys Lys Val Ile Thr Ser Trp Asp Gln Met Cys Ile Glu Lys Glu  
 20 25 30

Ala Asn Lys Thr Tyr Asn Cys Glu Asn Leu Gly Leu Ser Glu Ile Pro  
 35 40 45

Asp Thr Leu Pro Asn Thr Thr Glu Phe Leu Glu Phe Ser Phe Asn Phe  
 50 55 60

Leu Pro Thr Ile His Asn Arg Thr Phe Ser Arg Leu Met Asn Leu Thr  
 65 70 75 80

Phe Leu Asp Leu Thr Arg Cys Gln Ile Asn Trp Ile His Glu Asp Thr  
 85 90 95

Phe Gln Ser His His Gln Leu Ser Thr Leu Val Leu Thr Gly Asn Pro

100	105	110
Leu Ile Phe Met Ala Glu Thr Ser Leu Asn Gly Pro Lys Ser Leu Lys		
115	120	125
His Leu Phe Leu Ile Gln Thr Gly Ile Ser Asn Leu Glu Phe Ile Pro		
130	135	140
Val His Asn Leu Glu Asn Leu Glu Ser Leu Tyr Leu Gly Ser Asn His		
145	150	155
Ile Ser Ser Ile Lys Phe Pro Lys Asp Phe Pro Ala Arg Asn Leu Lys		
165	170	175
Val Leu Asp Phe Gln Asn Asn Ala Ile His Tyr Ile Ser Arg Glu Asp		
180	185	190
Met Arg Ser Leu Glu Gln Ala Ile Asn Leu Ser Leu Asn Phe Asn Gly		
195	200	205
Asn Asn Val Lys Gly Ile Glu Leu Gly Ala Phe Asp Ser Thr Ile Phe		
210	215	220
Gln Ser Leu Asn Phe Gly Gly Thr Pro Asn Leu Ser Val Ile Phe Asn		
225	230	235
Gly Leu Gln Asn Ser Thr Thr Gln Ser Leu Trp Leu Gly Thr Phe Glu		
245	250	255
Asp Ile Asp Asp Glu Asp Ile Ser Ser Ala Met Leu Lys Gly Leu Cys		
260	265	270
Glu Met Ser Val Glu Ser Leu Asn Leu Gln Glu His Arg Phe Ser Asp		
275	280	285
Ile Ser Ser Thr Thr Phe Gln Cys Phe Thr Gln Leu Gln Glu Leu Asp		
290	295	300
Leu Thr Ala Thr His Leu Lys Gly Leu Pro Ser Gly Met Lys Gly Leu		
305	310	315
Asn Leu Leu Lys Lys Leu Val Leu Ser Val Asn His Phe Asp Gln Leu		
325	330	335
Cys Gln Ile Ser Ala Ala Asn Phe Pro Ser Leu Thr His Leu Tyr Ile		
340	345	350

Arg Gly Asn Val Lys Lys Leu His Leu Gly Val Gly Cys Leu Glu Lys  
 355 360 365

Leu Gly Asn Leu Gln Thr Leu Asp Leu Ser His Asn Asp Ile Glu Ala  
 370 375 380

Ser Asp Cys Cys Ser Leu Gln Leu Lys Asn Leu Ser His Leu Gln Thr  
 385 390 395 400

Leu Asn Leu Ser His Asn Glu Pro Leu Gly Leu Gln Ser Gln Ala Phe  
 405 410 415

Lys Glu Cys Pro Gln Leu Glu Leu Leu Asp Leu Ala Phe Thr Arg Leu  
 420 425 430

His Ile Asn Ala Pro Gln Ser Pro Phe Gln Asn Leu His Phe Leu Gln  
 435 440 445

Val Leu Asn Leu Thr Tyr Cys Phe Leu Asp Thr Ser Asn Gln His Leu  
 450 455 460

Leu Ala Gly Leu Pro Val Leu Arg His Leu Asn Leu Lys Gly Asn His  
 465 470 475 480

Phe Gln Asp Gly Thr Ile Thr Lys Thr Asn Leu Leu Gln Thr Val Gly  
 485 490 495

Ser Leu Glu Val Leu Ile Leu Ser Ser Cys Gly Leu Leu Ser Ile Asp  
 500 505 510

Gln Gln Ala Phe His Ser Leu Gly Lys Met Ser His Val Asp Leu Ser  
 515 520 525

His Asn Ser Leu Thr Cys Asp Ser Ile Asp Ser Leu Ser His Leu Lys  
 530 535 540

Gly Ile Tyr Leu Asn Leu Ala Ala Asn Ser Ile Asn Ile Ile Ser Pro  
 545 550 555 560

Arg Leu Leu Pro Ile Leu Ser Gln Gln Ser Thr Ile Asn Leu Ser His  
 565 570 575

Asn Pro Leu Asp Cys Thr Cys Ser Asn Ile His Phe Leu Thr Trp Tyr  
 580 585 590

Lys Glu Asn Leu His Lys Leu Glu Gly Ser Glu Glu Thr Thr Cys Ala

595                      600                      605  
 Asn Pro Pro Ser Leu Arg Gly Val Lys Leu Ser Asp Val Lys Leu Ser  
 610                      615                      620  
 Cys Gly Ile Thr Ala Ile Gly Ile Phe Phe Leu Ile Val Phe Leu Leu  
 625                      630                      635                      640  
 Leu Leu Ala Ile Leu Leu Phe Phe Ala Val Lys Tyr Leu Leu Arg Trp  
 645                      650                      655  
 Lys Tyr Gln His Ile  
 660  
 <210> 69  
 <211> 614  
 <212> PRT  
 <213> Homo sapiens  
 <400> 69  
 Met Leu Ala Gly Gly Val Arg Ser Met Pro Ser Pro Leu Leu Ala Cys  
 1                      5                      10                      15  
 Trp Gln Pro Ile Leu Leu Leu Val Leu Gly Ser Val Leu Ser Gly Ser  
 20                      25                      30  
 Ala Thr Gly Cys Pro Pro Arg Cys Glu Cys Ser Ala Gln Asp Arg Ala  
 35                      40                      45  
 Val Leu Cys His Arg Lys Arg Phe Val Ala Val Pro Glu Gly Ile Pro  
 50                      55                      60  
 Thr Glu Thr Arg Leu Leu Asp Leu Gly Lys Asn Arg Ile Lys Thr Leu  
 65                      70                      75                      80  
 Asn Gln Asp Glu Phe Ala Ser Phe Pro His Leu Glu Glu Leu Glu Leu  
 85                      90                      95  
 Asn Glu Asn Ile Val Ser Ala Val Glu Pro Gly Ala Phe Asn Asn Leu  
 100                      105                      110  
 Phe Asn Leu Arg Thr Leu Gly Leu Arg Ser Asn Arg Leu Lys Leu Ile  
 115                      120                      125  
 Pro Leu Gly Val Phe Thr Gly Leu Ser Asn Leu Thr Lys Leu Asp Ile  
 130                      135                      140

Ser Glu Asn Lys Ile Val Ile Leu Leu Asp Tyr Met Phe Gln Asp Leu  
145 150 155 160

Tyr Asn Leu Lys Ser Leu Glu Val Gly Asp Asn Asp Leu Val Tyr Ile  
165 170 175

Ser His Arg Ala Phe Ser Gly Leu Asn Ser Leu Glu Gln Leu Thr Leu  
180 185 190

Glu Lys Cys Asn Leu Thr Ser Ile Pro Thr Glu Ala Leu Ser His Leu  
195 200 205

His Gly Leu Ile Val Leu Arg Leu Arg His Leu Asn Ile Asn Ala Ile  
210 215 220

Arg Asp Tyr Ser Phe Lys Arg Leu Tyr Arg Leu Lys Val Leu Glu Ile  
225 230 235 240

Ser His Trp Pro Tyr Leu Asp Thr Met Thr Pro Asn Cys Leu Tyr Gly  
245 250 255

Leu Asn Leu Thr Ser Leu Ser Ile Thr His Cys Asn Leu Thr Ala Val  
260 265 270

Pro Tyr Leu Ala Val Arg His Leu Val Tyr Leu Arg Phe Leu Asn Leu  
275 280 285

Ser Tyr Asn Pro Ile Ser Thr Ile Glu Gly Ser Met Leu His Glu Leu  
290 295 300

Leu Arg Leu Gln Glu Ile Gln Leu Val Gly Gly Gln Leu Ala Val Val  
305 310 315 320

Glu Pro Tyr Ala Phe Arg Gly Leu Asn Tyr Leu Arg Val Leu Asn Val  
325 330 335

Ser Gly Asn Gln Leu Thr Thr Leu Glu Glu Ser Val Phe His Ser Val  
340 345 350

Gly Asn Leu Glu Thr Leu Ile Leu Asp Ser Asn Pro Leu Ala Cys Asp  
355 360 365

Cys Arg Leu Leu Trp Val Phe Arg Arg Arg Trp Arg Leu Asn Phe Asn  
370 375 380

Arg Gln Gln Pro Thr Cys Ala Thr Pro Glu Phe Val Gln Gly Lys Glu  
385 390 395 400

Phe Lys Asp Phe Pro Asp Val Leu Leu Pro Asn Tyr Phe Thr Cys Arg  
 405 410 415

Arg Ala Arg Ile Arg Asp Arg Lys Ala Gln Gln Val Phe Val Asp Glu  
 420 425 430

Gly His Thr Val Gln Phe Val Cys Arg Ala Asp Gly Asp Pro Pro Pro  
 435 440 445

Ala Ile Leu Trp Leu Ser Pro Arg Lys His Leu Val Ser Ala Lys Ser  
 450 455 460

Asn Gly Arg Leu Thr Val Phe Pro Asp Gly Thr Leu Glu Val Arg Tyr  
 465 470 475 480

Ala Gln Val Gln Asp Asn Gly Thr Tyr Leu Cys Ile Ala Ala Asn Ala  
 485 490 495

Gly Gly Asn Asp Ser Met Pro Ala His Leu His Val Arg Ser Tyr Ser  
 500 505 510

Pro Asp Trp Pro His Gln Pro Asn Lys Thr Phe Ala Phe Ile Ser Asn  
 515 520 525

Gln Pro Gly Glu Gly Glu Ala Asn Ser Thr Arg Ala Thr Val Pro Phe  
 530 535 540

Pro Phe Asp Ile Lys Thr Leu Ile Ile Ala Thr Thr Met Gly Phe Ile  
 545 550 555 560

Ser Phe Leu Gly Val Val Leu Phe Cys Leu Val Leu Leu Phe Leu Trp  
 565 570 575

Ser Arg Gly Lys Gly Asn Thr Lys His Asn Ile Glu Ile Glu Tyr Val  
 580 585 590

Pro Arg Lys Ser Asp Ala Gly Ile Ser Ser Ala Asp Ala Pro Arg Lys  
 595 600 605

Phe Asn Met Lys Met Ile  
 610

<210> 70  
 <211> 428  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 70

Met Gln Glu Leu His Leu Leu Trp Trp Ala Leu Leu Leu Gly Leu Ala  
 1 5 10 15

Gln Ala Cys Pro Glu Pro Cys Asp Cys Gly Glu Lys Tyr Gly Phe Gln  
 20 25 30

Ile Ala Asp Cys Ala Tyr Arg Asp Leu Glu Ser Val Pro Pro Gly Phe  
 35 40 45

Pro Ala Asn Val Thr Thr Leu Ser Leu Ser Ala Asn Arg Leu Pro Gly  
 50 55 60

Leu Pro Glu Gly Ala Phe Arg Glu Val Pro Leu Leu Gln Ser Leu Trp  
 65 70 75 80

Leu Ala His Asn Glu Ile Arg Thr Val Ala Ala Gly Ala Leu Ala Ser  
 85 90 95

Leu Ser His Leu Lys Ser Leu Asp Leu Ser His Asn Leu Ile Ser Asp  
 100 105 110

Phe Ala Trp Ser Asp Leu His Asn Leu Ser Ala Leu Gln Leu Leu Lys  
 115 120 125

Met Asp Ser Asn Glu Leu Thr Phe Ile Pro Arg Asp Ala Phe Arg Ser  
 130 135 140

Leu Arg Ala Leu Arg Ser Leu Gln Leu Asn His Asn Arg Leu His Thr  
 145 150 155 160

Leu Ala Glu Gly Thr Phe Thr Pro Leu Thr Ala Leu Ser His Leu Gln  
 165 170 175

Ile Asn Glu Asn Pro Phe Asp Cys Thr Cys Gly Ile Val Trp Leu Lys  
 180 185 190

Thr Trp Ala Leu Thr Thr Ala Val Ser Ile Pro Glu Gln Asp Asn Ile  
 195 200 205

Ala Cys Thr Ser Pro His Val Leu Lys Gly Thr Pro Leu Ser Arg Leu  
 210 215 220

Pro Pro Leu Pro Cys Ser Ala Pro Ser Val Gln Leu Ser Tyr Gln Pro  
 225 230 235 240



Ser Gln Asp Gly Ala Glu Leu Arg Pro Gly Phe Val Leu Ala Leu His  
245 250 255

Cys Asp Val Asp Gly Gln Pro Ala Pro Gln Leu His Trp His Ile Gln  
260 265 270

Ile Pro Ser Gly Ile Val Glu Ile Thr Ser Pro Asn Val Gly Thr Asp  
275 280 285

Gly Arg Ala Leu Pro Gly Thr Pro Val Ala Ser Ser Gln Pro Arg Phe  
290 295 300

Gln Ala Phe Ala Asn Gly Ser Leu Leu Ile Pro Asp Phe Gly Lys Leu  
305 310 315 320

Glu Glu Gly Thr Tyr Ser Cys Leu Ala Thr Asn Glu Leu Gly Ser Ala  
325 330 335

Glu Ser Ser Val Asp Val Ala Leu Ala Thr Pro Gly Glu Gly Gly Glu  
340 345 350

Asp Thr Leu Gly Arg Arg Phe His Gly Lys Ala Val Glu Gly Lys Gly  
355 360 365

Cys Tyr Thr Val Asp Asn Glu Val Gln Pro Ser Gly Pro Glu Asp Asn  
370 375 380

Val Val Ile Ile Tyr Leu Ser Arg Ala Gly Asn Pro Glu Ala Ala Val  
385 390 395 400

Ala Glu Gly Val Pro Gly Gln Leu Pro Pro Gly Leu Leu Leu Leu Gly  
405 410 415

Gln Ser Leu Leu Leu Phe Phe Phe Leu Thr Ser Phe  
420 425

<210> 71  
<211> 612  
<212> PRT  
<213> Homo sapiens

<400> 71

Met Asp Val Ser Leu Cys Pro Ala Lys Cys Ser Phe Trp Arg Ile Phe  
1 5 10 15

Leu Leu Gly Ser Val Trp Leu Asp Tyr Val Gly Ser Val Leu Ala Cys  
20 25 30

Pro Ala Asn Cys Val Cys Ser Lys Thr Glu Ile Asn Cys Arg Arg Pro  
 35 40 45

Asp Asp Gly Asn Leu Phe Pro Leu Leu Glu Gly Gln Asp Ser Gly Asn  
 50 55 60

Ser Asn Gly Asn Ala Ser Ile Asn Ile Thr Asp Ile Ser Arg Asn Ile  
 65 70 75 80

Thr Ser Ile His Ile Glu Asn Trp Arg Ser Leu His Thr Leu Asn Ala  
 85 90 95

Val Asp Met Glu Leu Tyr Thr Gly Leu Gln Lys Leu Thr Ile Lys Asn  
 100 105 110

Ser Gly Leu Arg Ser Ile Gln Pro Arg Ala Phe Ala Lys Asn Pro His  
 115 120 125

Leu Arg Tyr Ile Asn Leu Ser Ser Asn Arg Leu Thr Thr Leu Ser Trp  
 130 135 140

Gln Leu Phe Gln Thr Leu Ser Leu Arg Glu Leu Gln Leu Glu Gln Asn  
 145 150 155 160

Phe Phe Asn Cys Ser Cys Asp Ile Arg Trp Met Gln Leu Trp Gln Glu  
 165 170 175

Gln Gly Glu Ala Lys Leu Asn Ser Gln Asn Leu Tyr Cys Ile Asn Ala  
 180 185 190

Asp Gly Ser Gln Leu Pro Leu Phe Arg Met Asn Ile Ser Gln Cys Asp  
 195 200 205

Leu Pro Glu Ile Ser Val Ser His Val Asn Leu Thr Val Arg Glu Gly  
 210 215 220

Asp Asn Ala Val Ile Thr Cys Asn Gly Ser Gly Ser Pro Leu Pro Asp  
 225 230 235 240

Val Asp Trp Ile Val Thr Gly Leu Gln Ser Ile Asn Thr His Gln Thr  
 245 250 255

Asn Leu Asn Trp Thr Asn Val His Ala Ile Asn Leu Thr Leu Val Asn  
 260 265 270

Val Thr Ser Glu Asp Asn Gly Phe Thr Leu Thr Cys Ile Ala Glu Asn  
 275 280 285

Val Val Gly Met Ser Asn Ala Ser Val Ala Leu Thr Val Tyr Tyr Pro  
 290 295 300

Pro Arg Val Val Ser Leu Glu Glu Pro Glu Leu Arg Leu Glu His Cys  
 305 310 315 320

Ile Glu Phe Val Val Arg Gly Asn Pro Pro Pro Thr Leu His Trp Leu  
 325 330 335

His Asn Gly Gln Pro Leu Arg Glu Ser Lys Ile Ile His Val Glu Tyr  
 340 345 350

Tyr Gln Glu Gly Glu Ile Ser Glu Gly Cys Leu Leu Phe Asn Lys Pro  
 355 360 365

Thr His Tyr Asn Asn Gly Asn Tyr Thr Leu Ile Ala Lys Asn Pro Leu  
 370 375 380

Gly Thr Ala Asn Gln Thr Ile Asn Gly His Phe Leu Lys Glu Pro Phe  
 385 390 395 400

Pro Glu Ser Thr Asp Asn Phe Ile Leu Phe Asp Glu Val Ser Pro Thr  
 405 410 415

Pro Pro Ile Thr Val Thr His Lys Pro Glu Glu Asp Thr Phe Gly Val  
 420 425 430

Ser Ile Ala Val Gly Leu Ala Ala Phe Ala Cys Val Leu Leu Val Val  
 435 440 445

Leu Phe Val Met Ile Asn Lys Tyr Gly Arg Arg Ser Lys Phe Gly Met  
 450 455 460

Lys Gly Pro Val Ala Val Ile Ser Gly Glu Glu Asp Ser Ala Ser Pro  
 465 470 475 480

Leu His His Ile Asn His Gly Ile Thr Thr Pro Ser Ser Leu Asp Ala  
 485 490 495

Gly Pro Asp Thr Val Val Ile Gly Met Thr Arg Ile Pro Val Ile Glu  
 500 505 510

Asn Pro Gln Tyr Phe Arg Gln Gly His Asn Cys His Lys Pro Asp Thr  
 515 520 525

Trp Val Phe Ser Asn Ile Asp Asn His Gly Ile Leu Asn Leu Lys Asp  
 530 535 540

Asn Arg Asp His Leu Val Pro Ser Thr His Tyr Ile Tyr Glu Glu Pro  
 545 550 555 560

Glu Val Gln Ser Gly Glu Val Ser Tyr Pro Arg Ser His Gly Phe Arg  
 565 570 575

Glu Ile Met Leu Asn Pro Ile Ser Leu Pro Gly His Ser Lys Pro Leu  
 580 585 590

Asn His Gly Ile Tyr Val Glu Asp Val Asn Val Tyr Phe Ser Lys Gly  
 595 600 605

Arg His Gly Phe  
 610

<210> 72  
 <211> 493  
 <212> PRT  
 <213> Homo sapiens

<400> 72

Met His Pro His Arg Asp Pro Arg Gly Leu Trp Leu Leu Leu Pro Ser  
 1 5 10 15

Leu Ser Leu Leu Leu Phe Glu Val Ala Arg Ala Gly Arg Ala Val Val  
 20 25 30

Ser Cys Pro Ala Ala Cys Leu Cys Ala Ser Asn Ile Leu Ser Cys Ser  
 35 40 45

Lys Gln Gln Leu Pro Asn Val Pro His Ser Leu Pro Ser Tyr Thr Ala  
 50 55 60

Leu Leu Asp Leu Ser His Asn Asn Leu Ser Arg Leu Arg Ala Glu Trp  
 65 70 75 80

Thr Pro Thr Arg Leu Thr Gln Leu His Ser Leu Leu Leu Ser His Asn  
 85 90 95

His Leu Asn Phe Ile Ser Ser Glu Ala Phe Ser Pro Val Pro Asn Leu  
 100 105 110

Arg Tyr Leu Asp Leu Ser Ser Asn Gln Leu Arg Thr Leu Asp Glu Phe

115	120	125
Leu Phe Ser Asp Leu Gln Val Leu Glu Val Leu Leu Leu Tyr Asn Asn		
130	135	140
His Ile Met Ala Val Asp Arg Cys Ala Phe Asp Asp Met Ala Gln Leu		
145	150	155
Gln Lys Leu Tyr Leu Ser Gln Asn Gln Ile Ser Arg Phe Pro Leu Glu		
165	170	175
Leu Val Lys Glu Gly Ala Lys Leu Pro Lys Leu Thr Leu Leu Asp Leu		
180	185	190
Ser Ser Asn Lys Leu Lys Asn Leu Pro Leu Pro Asp Leu Gln Lys Leu		
195	200	205
Pro Ala Trp Ile Lys Asn Gly Leu Tyr Leu His Asn Asn Pro Leu Asn		
210	215	220
Cys Asp Cys Glu Leu Tyr Gln Leu Phe Ser His Trp Gln Tyr Arg Gln		
225	230	235
Leu Ser Ser Val Met Asp Phe Gln Glu Asp Leu Tyr Cys Met Asn Ser		
245	250	255
Lys Lys Leu His Asn Val Phe Asn Leu Ser Phe Leu Asn Cys Gly Glu		
260	265	270
Tyr Lys Glu Arg Ala Trp Glu Ala His Leu Gly Asp Thr Leu Ile Ile		
275	280	285
Lys Cys Asp Thr Lys Gln Gln Gly Met Thr Lys Val Trp Val Thr Pro		
290	295	300
Ser Asn Glu Arg Val Leu Asp Glu Val Thr Asn Gly Thr Val Ser Val		
305	310	315
Ser Lys Asp Gly Ser Leu Leu Phe Gln Gln Val Gln Val Glu Asp Gly		
325	330	335
Gly Val Tyr Thr Cys Tyr Ala Met Gly Glu Thr Phe Asn Glu Thr Leu		
340	345	350
Ser Val Glu Leu Lys Val His Asn Phe Thr Leu His Gly His His Asp		
355	360	365

Thr Leu Asn Thr Ala Tyr Thr Thr Leu Val Gly Cys Ile Leu Ser Val  
 370 375 380

Val Leu Val Leu Ile Tyr Leu Tyr Leu Thr Pro Cys Arg Cys Trp Cys  
 385 390 395 400

Arg Gly Val Glu Lys Pro Ser Ser His Gln Gly Asp Ser Leu Ser Ser  
 405 410 415

Ser Met Leu Ser Thr Thr Pro Asn His Asp Pro Met Ala Gly Gly Asp  
 420 425 430

Lys Asp Asp Gly Phe Asp Arg Arg Val Ala Phe Leu Glu Pro Ala Gly  
 435 440 445

Pro Gly Gln Gly Gln Asn Gly Lys Leu Lys Pro Gly Asn Thr Leu Pro  
 450 455 460

Val Pro Glu Ala Thr Gly Lys Gly Gln Arg Arg Met Ser Asp Pro Glu  
 465 470 475 480

Ser Val Ser Ser Val Phe Ser Asp Thr Pro Ile Val Val  
 485 490

<210> 73  
 <211> 616  
 <212> PRT  
 <213> Homo sapiens

<400> 73

Met Asn His Asn Arg Leu Gly Ser Leu Pro Arg Asp Ala Leu Gly Ala  
 1 5 10 15

Leu Pro Asp Leu Arg Ser Leu Arg Ile Asn Asn Asn Arg Leu Arg Thr  
 20 25 30

Leu Ala Pro Gly Thr Phe Asp Ala Leu Ser Ala Leu Ser His Leu Gln  
 35 40 45

Leu Tyr His Asn Pro Phe His Cys Gly Cys Gly Leu Val Trp Leu Gln  
 50 55 60

Ala Trp Ala Ala Ser Thr Arg Val Ser Leu Pro Glu Pro Asp Ser Ile  
 65 70 75 80

Ala Cys Ala Ser Pro Pro Ala Leu Gln Gly Val Pro Val Tyr Arg Leu  
 85 90 95

Pro Ala Leu Pro Cys Ala Pro Pro Ser Val His Leu Ser Ala Glu Pro  
                   100                                  105                                  110

Pro Leu Glu Ala Pro Gly Thr Pro Leu Arg Ala Gly Leu Ala Phe Val  
                   115                                  120                                  125

Leu His Cys Ile Ala Asp Gly His Pro Thr Pro Arg Leu Gln Trp Gln  
                   130                                  135                                  140

Leu Gln Ile Pro Gly Gly Thr Val Val Leu Glu Pro Pro Val Leu Ser  
                   145                                  150                                  155                                  160

Gly Glu Asp Asp Gly Val Gly Ala Glu Glu Gly Glu Gly Glu Gly Asp  
                                   165                                  170                                  175

Gly Asp Leu Leu Thr Gln Thr Gln Ala Gln Thr Pro Thr Pro Ala Pro  
                   180                                  185                                  190

Ala Trp Pro Ala Pro Pro Ala Thr Pro Arg Phe Leu Ala Leu Ala Asn  
                   195                                  200                                  205

Gly Ser Leu Leu Val Pro Leu Leu Ser Ala Lys Glu Ala Gly Val Tyr  
                   210                                  215                                  220

Thr Cys Arg Ala His Asn Glu Leu Gly Ala Asn Ser Thr Ser Ile Arg  
                   225                                  230                                  235                                  240

Val Ala Val Ala Ala Thr Gly Pro Pro Lys His Ala Pro Gly Ala Gly  
                                   245                                  250                                  255

Gly Glu Pro Asp Gly Gln Ala Pro Thr Ser Glu Arg Lys Ser Thr Ala  
                   260                                  265                                  270

Lys Gly Arg Gly Asn Ser Val Leu Pro Ser Lys Pro Glu Gly Lys Ile  
                   275                                  280                                  285

Lys Gly Gln Gly Leu Ala Lys Val Ser Ile Leu Gly Glu Thr Glu Thr  
                   290                                  295                                  300

Glu Pro Glu Glu Asp Thr Ser Glu Gly Glu Glu Ala Glu Asp Gln Ile  
                   305                                  310                                  315                                  320

Leu Ala Asp Pro Ala Glu Glu Gln Arg Cys Gly Asn Gly Asp Pro Ser  
                                   325                                  330                                  335

Arg Tyr Val Ser Asn His Ala Phe Asn Gln Ser Ala Glu Leu Lys Pro  
 340 345 350

His Val Phe Glu Leu Gly Val Ile Ala Leu Asp Val Ala Glu Arg Glu  
 355 360 365

Ala Arg Val Gln Leu Thr Pro Leu Ala Ala Arg Trp Gly Pro Gly Pro  
 370 375 380

Gly Gly Ala Gly Gly Ala Pro Arg Pro Gly Arg Arg Pro Leu Arg Leu  
 385 390 395 400

Leu Tyr Leu Cys Pro Ala Gly Gly Gly Ala Ala Val Gln Trp Ser Arg  
 405 410 415

Val Glu Glu Gly Val Asn Ala Tyr Trp Phe Arg Gly Leu Arg Pro Gly  
 420 425 430

Thr Asn Tyr Ser Val Cys Leu Ala Leu Ala Gly Glu Ala Cys His Val  
 435 440 445

Gln Val Val Phe Ser Thr Lys Lys Glu Leu Pro Ser Leu Leu Val Ile  
 450 455 460

Val Ala Val Ser Val Phe Leu Leu Val Leu Ala Thr Val Pro Leu Leu  
 465 470 475 480

Gly Ala Ala Cys Cys His Leu Leu Ala Lys His Pro Gly Lys Pro Tyr  
 485 490 495

Arg Leu Ile Leu Arg Pro Gln Ala Pro Asp Pro Met Glu Lys Arg Ile  
 500 505 510

Ala Ala Asp Phe Asp Pro Arg Ala Ser Tyr Leu Glu Ser Glu Lys Ser  
 515 520 525

Tyr Pro Ala Gly Gly Glu Ala Gly Gly Glu Glu Pro Glu Asp Val Gln  
 530 535 540

Gly Glu Gly Leu Asp Glu Asp Ala Glu Gln Gly Asp Pro Ser Gly Asp  
 545 550 555 560

Leu Gln Arg Glu Glu Ser Leu Ala Ala Cys Ser Leu Val Glu Ser Gln  
 565 570 575

Ser Lys Ala Asn Gln Glu Glu Phe Glu Ala Gly Ser Glu Tyr Ser Asp  
 580 585 590



Arg Leu Pro Leu Gly Ala Glu Ala Val Asn Ile Ala Gln Glu Ile Asn  
 595 600 605

Gly Asn Tyr Arg Gln Thr Ala Gly  
 610 615

<210> 74  
 <211> 504  
 <212> PRT  
 <213> Homo sapiens  
 <400> 74

Met Thr Trp Leu Val Leu Leu Gly Thr Leu Leu Cys Met Leu Arg Val  
 1 5 10 15

Gly Leu Gly Thr Pro Asp Ser Glu Gly Phe Pro Pro Arg Ala Leu His  
 20 25 30

Asn Cys Pro Tyr Lys Cys Ile Cys Ala Ala Asp Leu Leu Ser Cys Thr  
 35 40 45

Gly Leu Gly Leu Gln Asp Val Pro Ala Glu Leu Pro Ala Ala Thr Ala  
 50 55 60

Asp Leu Asp Leu Ser His Asn Ala Leu Gln Arg Leu Arg Pro Gly Trp  
 65 70 75 80

Leu Ala Pro Leu Phe Gln Leu Arg Ala Leu His Leu Asp His Asn Glu  
 85 90 95

Leu Asp Ala Leu Gly Arg Gly Val Phe Val Asn Ala Ser Gly Leu Arg  
 100 105 110

Leu Leu Asp Leu Ser Ser Asn Thr Leu Arg Ala Leu Gly Arg His Asp  
 115 120 125

Leu Asp Gly Leu Gly Ala Leu Glu Lys Leu Leu Leu Phe Asn Asn Arg  
 130 135 140

Leu Val His Leu Asp Glu His Ala Phe His Gly Leu Arg Ala Leu Ser  
 145 150 155 160

His Leu Tyr Leu Gly Cys Asn Glu Leu Ala Ser Phe Ser Phe Asp His  
 165 170 175

Leu His Gly Leu Ser Ala Thr His Leu Leu Thr Leu Asp Leu Ser Ser

180	185	190
Asn Arg Leu Gly His Ile Ser Val Pro Glu Leu Ala Ala Leu Pro Ala 195 200 205		
Phe Leu Lys Asn Gly Leu Tyr Leu His Asn Asn Pro Leu Pro Cys Asp 210 215 220		
Cys Arg Leu Tyr His Leu Leu Gln Arg Trp His Gln Arg Gly Leu Ser 225 230 235 240		
Ala Val Arg Asp Phe Ala Arg Glu Tyr Val Cys Leu Ala Phe Lys Val 245 250 255		
Pro Ala Ser Arg Val Arg Phe Phe Gln His Ser Arg Val Phe Glu Asn 260 265 270		
Cys Ser Ser Ala Pro Ala Leu Gly Leu Glu Arg Pro Glu Glu His Leu 275 280 285		
Tyr Ala Leu Val Gly Arg Ser Leu Arg Leu Tyr Cys Asn Thr Ser Val 290 295 300		
Pro Ala Met Arg Ile Ala Trp Val Ser Pro Gln Gln Glu Leu Leu Arg 305 310 315 320		
Ala Pro Gly Ser Arg Asp Gly Ser Ile Ala Val Leu Ala Asp Gly Ser 325 330 335		
Leu Ala Ile Gly Asn Val Gln Glu Gln His Ala Gly Leu Phe Val Cys 340 345 350		
Leu Ala Thr Gly Pro Arg Leu His His Asn Gln Thr His Glu Tyr Asn 355 360 365		
Val Ser Val His Phe Pro Arg Pro Glu Pro Glu Ala Phe Asn Thr Gly 370 375 380		
Phe Thr Thr Leu Leu Gly Cys Ala Val Gly Leu Val Leu Val Leu Leu 385 390 395 400		
Tyr Leu Phe Ala Pro Pro Cys Arg Cys Cys Arg Arg Ala Cys Arg Cys 405 410 415		
Arg Arg Trp Pro Gln Thr Pro Ser Pro Leu Gln Glu Leu Ser Ala Gln 420 425 430		

Ser Ser Val Leu Ser Thr Thr Pro Pro Asp Ala Pro Ser Arg Lys Ala  
 435 440 445

Ser Val His Lys His Val Val Phe Leu Glu Pro Gly Arg Arg Gly Leu  
 450 455 460

Asn Gly Arg Val Gln Leu Ala Val Ala Glu Glu Phe Asp Leu Tyr Asn  
 465 470 475 480

Pro Gly Gly Leu Gln Leu Lys Ala Gly Ser Glu Ser Ala Ser Ser Ile  
 485 490 495

Gly Ser Glu Gly Pro Met Thr Thr  
 500

<210> 75  
 <211> 623  
 <212> PRT  
 <213> Homo sapiens  
 <400> 75

Met Arg Val Ala Leu Gly Met Leu Trp Leu Leu Ala Leu Ala Trp Pro  
 1 5 10 15

Pro Gln Ala Arg Gly Phe Cys Pro Ser Gln Cys Ser Cys Ser Leu His  
 20 25 30

Ile Met Gly Asp Gly Ser Lys Ala Arg Thr Val Val Cys Asn Asp Pro  
 35 40 45

Asp Met Thr Leu Pro Pro Ala Ser Ile Pro Pro Asp Thr Ser Arg Leu  
 50 55 60

Arg Leu Glu Arg Thr Ala Ile Arg Arg Val Pro Gly Glu Ala Phe Arg  
 65 70 75 80

Pro Leu Gly Arg Leu Glu Gln Leu Trp Leu Pro Tyr Asn Ala Leu Ser  
 85 90 95

Glu Leu Asn Ala Leu Met Leu Arg Gly Leu Arg Arg Leu Arg Glu Leu  
 100 105 110

Arg Leu Pro Gly Asn Arg Leu Ala Ala Phe Pro Trp Ala Ala Leu Arg  
 115 120 125

Asp Ala Pro Lys Leu Arg Leu Leu Asp Leu Gln Ala Asn Arg Leu Ser  
 130 135 140

Ala Val Pro Ala Glu Ala Ala Arg Phe Leu Glu Asn Leu Thr Phe Leu  
 145 150 155 160

Asp Leu Ser Ser Asn Gln Leu Met Arg Leu Pro Gln Glu Leu Ile Val  
 165 170 175

Ser Trp Ala His Leu Glu Thr Gly Ile Phe Pro Pro Gly His His Pro  
 180 185 190

Arg Arg Val Leu Gly Leu Gln Asp Asn Pro Trp Ala Cys Asp Cys Arg  
 195 200 205

Leu Tyr Asp Leu Val His Leu Leu Asp Gly Trp Ala Pro Asn Leu Ala  
 210 215 220

Phe Ile Glu Thr Glu Leu Arg Cys Ala Ser Pro Arg Ser Leu Ala Gly  
 225 230 235 240

Val Ala Phe Ser Gln Leu Glu Leu Arg Lys Cys Gln Gly Pro Glu Leu  
 245 250 255

His Pro Gly Val Ala Ser Ile Arg Ser Leu Leu Gly Gly Thr Ala Leu  
 260 265 270

Leu Arg Cys Gly Ala Thr Gly Val Pro Gly Pro Glu Met Ser Trp Arg  
 275 280 285

Arg Ala Asn Gly Arg Pro Leu Asn Gly Thr Val His Gln Glu Val Ser  
 290 295 300

Ser Asp Gly Thr Ser Trp Thr Leu Leu Gly Leu Pro Ala Val Ser His  
 305 310 315 320

Leu Asp Ser Gly Asp Tyr Ile Cys Gln Ala Lys Asn Phe Leu Gly Ala  
 325 330 335

Ser Glu Thr Val Ile Ser Leu Ile Val Thr Glu Pro Pro Thr Ser Thr  
 340 345 350

Glu His Ser Gly Ser Pro Gly Ala Leu Trp Ala Arg Thr Gly Gly Gly  
 355 360 365

Gly Glu Ala Ala Ala Tyr Asn Asn Lys Leu Val Ala Arg His Val Pro  
 370 375 380

Gln Ile Pro Lys Pro Ala Val Leu Ala Thr Gly Pro Ser Val Pro Ser  
385 390 395 400

Thr Lys Glu Glu Leu Thr Leu Glu His Phe Gln Met Asp Ala Leu Gly  
405 410 415

Glu Leu Ser Asp Gly Arg Ala Gly Pro Ser Glu Ala Arg Met Val Arg  
420 425 430

Ser Val Lys Val Val Gly Asp Thr Tyr His Ser Val Ser Leu Val Trp  
435 440 445

Lys Ala Pro Gln Ala Lys Asn Thr Thr Ala Phe Ser Val Leu Tyr Ala  
450 455 460

Val Phe Gly Gln His Ser Met Arg Arg Val Ile Val Gln Pro Gly Lys  
465 470 475 480

Thr Arg Val Thr Ile Thr Gly Leu Leu Pro Lys Thr Lys Tyr Val Ala  
485 490 495

Cys Val Cys Val Gln Gly Leu Val Pro Arg Lys Glu Gln Cys Val Ile  
500 505 510

Phe Ser Thr Asn Glu Val Val Asp Ala Glu Asn Thr Gln Gln Leu Ile  
515 520 525

Asn Val Val Val Ile Ser Val Ala Ile Val Ile Ala Leu Pro Leu Thr  
530 535 540

Leu Leu Val Cys Cys Ser Ala Leu Gln Lys Arg Cys Arg Lys Cys Phe  
545 550 555 560

Asn Lys Asp Ser Thr Glu Ala Thr Val Thr Tyr Val Asn Leu Glu Arg  
565 570 575

Leu Gly Tyr Ser Glu Asp Gly Leu Glu Glu Leu Ser Arg His Ser Val  
580 585 590

Ser Glu Ala Asp Arg Leu Leu Ser Ala Arg Ser Ser Val Asp Phe Gln  
595 600 605

Ala Phe Gly Val Lys Gly Gly Arg Arg Ile Asn Glu Tyr Phe Cys  
610 615 620

<210> 76

<211> 789

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 76

Met Glu Thr Leu Leu Gly Gly Leu Leu Ala Phe Gly Met Ala Phe Ala  
 1 5 10 15

Val Val Asp Ala Cys Pro Lys Tyr Cys Val Cys Gln Asn Leu Ser Glu  
 20 25 30

Ser Leu Gly Thr Leu Cys Pro Ser Lys Gly Leu Leu Phe Val Pro Pro  
 35 40 45

Asp Ile Asp Arg Arg Thr Val Glu Leu Arg Leu Gly Gly Asn Phe Ile  
 50 55 60

Ile His Ile Ser Arg Gln Asp Phe Ala Asn Met Thr Gly Leu Val Asp  
 65 70 75 80

Leu Thr Leu Ser Arg Asn Thr Ile Ser His Ile Gln Pro Phe Ser Phe  
 85 90 95

Leu Asp Leu Glu Ser Leu Arg Ser Leu His Leu Asp Ser Asn Arg Leu  
 100 105 110

Pro Ser Leu Gly Glu Asp Thr Leu Arg Gly Leu Val Asn Leu Gln His  
 115 120 125

Leu Ile Val Asn Asn Asn Gln Leu Gly Gly Ile Ala Asp Glu Ala Phe  
 130 135 140

Glu Asp Phe Leu Leu Thr Leu Glu Asp Leu Asp Leu Ser Tyr Asn Asn  
 145 150 155 160

Leu His Gly Leu Pro Trp Asp Ser Val Arg Arg Met Val Asn Leu His  
 165 170 175

Gln Leu Ser Leu Asp His Asn Leu Leu Asp His Ile Ala Glu Gly Thr  
 180 185 190

Phe Ala Asp Leu Gln Lys Leu Ala Arg Leu Asp Leu Thr Ser Asn Arg  
 195 200 205

Leu Gln Lys Leu Pro Pro Asp Pro Ile Phe Ala Arg Ser Gln Ala Ser  
 210 215 220

Ala Leu Thr Ala Thr Pro Phe Ala Pro Pro Leu Ser Phe Ser Phe Gly

225	230	235	240
Gly Asn Pro Leu His Cys Asn Cys Glu Leu Leu Trp Leu Arg Arg Leu	245	250	255
Glu Arg Asp Asp Asp Leu Glu Thr Cys Gly Ser Pro Gly Gly Leu Lys	260	265	270
Gly Arg Tyr Phe Trp His Val Arg Glu Glu Glu Phe Val Cys Glu Pro	275	280	285
Pro Leu Ile Thr Gln His Thr His Lys Leu Leu Val Leu Glu Gly Gln	290	295	300
Ala Ala Thr Leu Lys Cys Lys Ala Ile Gly Asp Pro Ser Pro Leu Ile	305	310	315
His Trp Val Ala Pro Asp Asp Arg Leu Val Gly Asn Ser Ser Arg Thr	325	330	335
Ala Val Tyr Asp Asn Gly Thr Leu Asp Ile Phe Ile Thr Thr Ser Gln	340	345	350
Asp Ser Gly Ala Phe Thr Cys Ile Ala Ala Asn Ala Ala Gly Glu Ala	355	360	365
Thr Ala Met Val Glu Val Ser Ile Val Gln Leu Pro His Leu Ser Asn	370	375	380
Ser Thr Ser Arg Thr Ala Pro Pro Lys Ser Arg Leu Ser Asp Ile Thr	385	390	395
Gly Ser Ser Lys Thr Ser Arg Gly Gly Gly Gly Ser Gly Gly Gly Glu	405	410	415
Pro Pro Lys Ser Pro Pro Glu Arg Ala Val Leu Val Ser Glu Val Thr	420	425	430
Thr Thr Ser Ala Leu Val Lys Trp Ser Val Ser Lys Ser Ala Pro Arg	435	440	445
Val Lys Met Tyr Gln Leu Gln Tyr Asn Cys Ser Asp Asp Glu Val Leu	450	455	460
Ile Tyr Arg Met Ile Pro Ala Ser Asn Lys Ala Phe Val Val Asn Asn	465	470	475
			480

Leu Val Ser Gly Thr Gly Tyr Asp Leu Cys Val Leu Ala Met Trp Asp  
 485 490 495

Asp Thr Ala Thr Thr Leu Thr Ala Thr Asn Ile Val Gly Cys Ala Gln  
 500 505 510

Phe Phe Thr Lys Ala Asp Tyr Pro Gln Cys Gln Ser Met His Ser Gln  
 515 520 525

Ile Leu Gly Gly Thr Met Ile Leu Val Ile Gly Gly Ile Ile Val Ala  
 530 535 540

Thr Leu Leu Val Phe Ile Val Ile Leu Met Val Arg Tyr Lys Val Cys  
 545 550 555 560

Asn His Glu Ala Pro Ser Lys Met Ala Ala Ala Val Ser Asn Val Tyr  
 565 570 575

Ser Gln Thr Asn Gly Ala Gln Pro Pro Pro Pro Ser Ser Ala Pro Ala  
 580 585 590

Gly Ala Pro Pro Gln Gly Pro Pro Lys Val Val Val Arg Asn Glu Leu  
 595 600 605

Leu Asp Phe Thr Ala Ser Leu Ala Arg Ala Ser Asp Ser Ser Ser Ser  
 610 615 620

Ser Ser Leu Gly Ser Gly Glu Ala Ala Gly Leu Gly Arg Ala Pro Trp  
 625 630 635 640

Arg Ile Pro Pro Ser Ala Pro Arg Pro Lys Pro Ser Leu Asp Arg Leu  
 645 650 655

Met Gly Ala Phe Ala Ser Leu Asp Leu Lys Ser Gln Arg Lys Glu Glu  
 660 665 670

Leu Leu Asp Ser Arg Thr Pro Ala Gly Arg Gly Ala Gly Thr Ser Ala  
 675 680 685

Arg Gly His His Ser Asp Arg Glu Pro Leu Leu Gly Pro Pro Ala Ala  
 690 695 700

Arg Ala Arg Ser Leu Leu Pro Leu Pro Leu Glu Gly Lys Ala Lys Arg  
 705 710 715 720

Ser His Ser Phe Asp Met Gly Asp Phe Ala Ala Ala Ala Gly Gly



	725		730		735
Val Val Pro Gly Gly Tyr Ser Pro Pro Arg Lys Val Ser Asn Ile Trp					
	740		745		750
Thr Lys Arg Ser Leu Ser Val Asn Gly Met Leu Leu Pro Phe Glu Glu					
	755		760		765
Ser Asp Leu Val Gly Ala Arg Gly Thr Phe Gly Ser Ser Glu Trp Val					
	770		775		780
Met Glu Ser Thr Val					
	785				
<210> 77					
<211> 628					
<212> PRT					
<213> Homo sapiens					
<400> 77					
Met Ala Ile Leu Pro Leu Leu Leu Cys Leu Leu Pro Leu Ala Pro Ala					
1	5		10		15
Ser Ser Pro Pro Gln Ser Ala Thr Pro Ser Pro Cys Pro Arg Arg Cys					
	20		25		30
Arg Cys Gln Thr Gln Ser Leu Pro Leu Ser Val Leu Cys Pro Gly Ala					
	35		40		45
Gly Leu Leu Phe Val Pro Pro Ser Leu Asp Arg Arg Ala Ala Glu Leu					
	50		55		60
Arg Leu Ala Asp Asn Phe Ile Ala Ser Val Arg Arg Arg Asp Leu Ala					
	65		70		75
Asn Met Thr Gly Leu Leu His Leu Ser Leu Ser Arg Asn Thr Ile Arg					
	85		90		95
His Val Ala Ala Gly Ala Phe Ala Asp Leu Arg Ala Leu Arg Ala Leu					
	100		105		110
His Leu Asp Gly Asn Arg Leu Thr Ser Leu Gly Glu Gly Gln Leu Arg					
	115		120		125
Gly Leu Val Asn Leu Arg His Leu Ile Leu Ser Asn Asn Gln Leu Ala					
	130		135		140

Ala Leu Ala Ala Gly Ala Leu Asp Asp Cys Ala Glu Thr Leu Glu Asp  
 145 150 155 160

Leu Asp Leu Ser Tyr Asn Asn Leu Glu Gln Leu Pro Trp Glu Ala Leu  
 165 170 175

Gly Arg Leu Gly Asn Val Asn Thr Leu Gly Leu Asp His Asn Leu Leu  
 180 185 190

Ala Ser Val Pro Ala Gly Ala Phe Ser Arg Leu His Lys Leu Ala Arg  
 195 200 205

Leu Asp Met Thr Ser Asn Arg Leu Thr Thr Ile Pro Pro Asp Pro Leu  
 210 215 220

Phe Ser Arg Leu Pro Leu Leu Ala Arg Pro Arg Gly Ser Pro Ala Ser  
 225 230 235 240

Ala Leu Val Leu Ala Phe Gly Gly Asn Pro Leu His Cys Asn Cys Glu  
 245 250 255

Leu Val Trp Leu Arg Arg Leu Ala Arg Glu Asp Asp Leu Glu Ala Cys  
 260 265 270

Ala Ser Pro Pro Ala Leu Gly Gly Arg Tyr Phe Trp Ala Val Gly Glu  
 275 280 285

Glu Glu Phe Val Cys Glu Pro Pro Val Val Thr His Arg Ser Pro Pro  
 290 295 300

Leu Ala Val Pro Ala Gly Arg Pro Ala Ala Leu Arg Cys Arg Ala Val  
 305 310 315 320

Gly Asp Pro Glu Pro Arg Val Arg Trp Val Ser Pro Gln Gly Arg Leu  
 325 330 335

Leu Gly Asn Ser Ser Arg Ala Arg Ala Phe Pro Asn Gly Thr Leu Glu  
 340 345 350

Leu Leu Val Thr Glu Pro Gly Asp Gly Gly Ile Phe Thr Cys Ile Ala  
 355 360 365

Ala Asn Ala Ala Gly Glu Ala Thr Ala Ala Val Glu Leu Thr Val Gly  
 370 375 380

Pro Pro Pro Pro Pro Gln Leu Ala Asn Ser Thr Ser Cys Asp Pro Pro  
 385 390 395 400

Arg Asp Gly Asp Pro Asp Ala Leu Thr Pro Pro Ser Ala Ala Ser Ala  
 405 410 415

Ser Ala Lys Val Ala Asp Thr Gly Pro Pro Thr Asp Arg Gly Val Gln  
 420 425 430

Val Thr Glu His Gly Ala Thr Ala Ala Leu Val Gln Trp Pro Asp Gln  
 435 440 445

Arg Pro Ile Pro Gly Ile Arg Met Tyr Gln Ile Gln Tyr Asn Ser Ser  
 450 455 460

Ala Asp Asp Ile Leu Val Tyr Arg Met Ile Pro Ala Glu Ser Arg Ser  
 465 470 475 480

Phe Leu Leu Thr Asp Leu Ala Ser Gly Arg Thr Tyr Asp Leu Cys Val  
 485 490 495

Leu Ala Val Tyr Glu Asp Ser Ala Thr Gly Leu Thr Ala Thr Arg Pro  
 500 505 510

Val Gly Cys Ala Arg Phe Ser Thr Glu Pro Ala Leu Arg Pro Cys Gly  
 515 520 525

Ala Pro His Ala Pro Phe Leu Gly Gly Thr Met Ile Ile Ala Leu Gly  
 530 535 540

Gly Val Ile Val Ala Ser Val Leu Val Phe Ile Phe Val Leu Leu Met  
 545 550 555 560

Arg Tyr Lys Val His Gly Gly Gln Pro Pro Gly Lys Ala Lys Ile Pro  
 565 570 575

Ala Pro Val Ser Ser Val Cys Ser Gln Thr Asn Gly Ala Leu Gly Pro  
 580 585 590

Thr Pro Thr Pro Ala Pro Pro Ala Pro Glu Pro Ala Ala Leu Arg Ala  
 595 600 605

His Thr Val Val Gln Leu Asp Cys Glu Pro Trp Gly Pro Gly His Glu  
 610 615 620

Pro Val Gly Pro  
 625

<210> 78  
 <211> 673  
 <212> PRT  
 <213> Homo sapiens

<400> 78

Met Cys Ser Arg Val Pro Leu Leu Leu Pro Leu Leu Leu Leu Leu Ala  
 1 5 10 15

Leu Gly Pro Gly Val Gln Gly Cys Pro Ser Gly Cys Gln Cys Ser Gln  
 20 25 30

Pro Gln Thr Val Phe Cys Thr Ala Arg Gln Gly Thr Thr Val Pro Arg  
 35 40 45

Asp Val Pro Pro Asp Thr Val Gly Leu Tyr Val Phe Glu Asn Gly Ile  
 50 55 60

Thr Met Leu Asp Ala Gly Ser Phe Ala Gly Leu Pro Gly Leu Gln Leu  
 65 70 75 80

Leu Asp Leu Ser Gln Asn Gln Ile Ala Ser Leu Pro Ser Gly Val Phe  
 85 90 95

Gln Pro Leu Ala Asn Leu Ser Asn Leu Asp Leu Thr Ala Asn Arg Leu  
 100 105 110

His Glu Ile Thr Asn Glu Thr Phe Arg Gly Leu Arg Arg Leu Glu Arg  
 115 120 125

Leu Tyr Leu Gly Lys Asn Arg Ile Arg His Ile Gln Pro Gly Ala Phe  
 130 135 140

Asp Thr Leu Asp Arg Leu Leu Glu Leu Lys Leu Gln Asp Asn Glu Leu  
 145 150 155 160

Arg Ala Leu Pro Pro Leu Arg Leu Pro Arg Leu Leu Leu Leu Asp Leu  
 165 170 175

Ser His Asn Ser Leu Leu Ala Leu Glu Pro Gly Ile Leu Asp Thr Ala  
 180 185 190

Asn Val Glu Ala Leu Arg Leu Ala Gly Leu Gly Leu Gln Gln Leu Asp  
 195 200 205

Glu Gly Leu Phe Ser Arg Leu Arg Asn Leu His Asp Leu Asp Val Ser  
 210 215 220

Asp Asn Gln Leu Glu Arg Val Pro Pro Val Ile Arg Gly Leu Arg Gly  
 225 230 235 240

Leu Thr Arg Leu Arg Leu Ala Gly Asn Thr Arg Ile Ala Gln Leu Arg  
 245 250 255

Pro Glu Asp Leu Ala Gly Leu Ala Ala Leu Gln Glu Leu Asp Val Ser  
 260 265 270

Asn Leu Ser Leu Gln Ala Leu Pro Gly Asp Leu Ser Gly Leu Phe Pro  
 275 280 285

Arg Leu Arg Leu Leu Ala Ala Ala Arg Asn Pro Phe Asn Cys Val Cys  
 290 295 300

Pro Leu Ser Trp Phe Gly Pro Trp Val Arg Glu Ser His Val Thr Leu  
 305 310 315 320

Ala Ser Pro Glu Glu Thr Arg Cys His Phe Pro Pro Lys Asn Ala Gly  
 325 330 335

Arg Leu Leu Leu Glu Leu Asp Tyr Ala Asp Phe Gly Cys Pro Ala Thr  
 340 345 350

Thr Thr Thr Ala Thr Val Pro Thr Thr Arg Pro Val Val Arg Glu Pro  
 355 360 365

Thr Ala Leu Ser Ser Ser Leu Ala Pro Thr Trp Leu Ser Pro Thr Glu  
 370 375 380

Pro Ala Thr Glu Ala Pro Ser Pro Pro Ser Thr Ala Pro Pro Thr Val  
 385 390 395 400

Gly Pro Val Pro Gln Pro Gln Asp Cys Pro Pro Ser Thr Cys Leu Asn  
 405 410 415

Gly Gly Thr Cys His Leu Gly Thr Arg His His Leu Ala Cys Leu Cys  
 420 425 430

Pro Glu Gly Phe Thr Gly Leu Tyr Cys Glu Ser Gln Met Gly Gln Gly  
 435 440 445

Thr Arg Pro Ser Pro Thr Pro Val Thr Pro Arg Pro Pro Arg Ser Leu  
 450 455 460

Thr Leu Gly Ile Glu Pro Val Ser Pro Thr Ser Leu Arg Val Gly Leu

465                      470                      475                      480  
 Gln Arg Tyr Leu Gln Gly Ser Ser Val Gln Leu Arg Ser Leu Arg Leu  
                                  485                      490                      495  
 Thr Tyr Arg Asn Leu Ser Gly Pro Asp Lys Arg Leu Val Thr Leu Arg  
                                  500                      505                      510  
 Leu Pro Ala Ser Leu Ala Glu Tyr Thr Val Thr Gln Leu Arg Pro Asn  
                                  515                      520                      525  
 Ala Thr Tyr Ser Val Cys Val Met Pro Leu Gly Pro Gly Arg Val Pro  
                                  530                      535                      540  
 Glu Gly Glu Glu Ala Cys Gly Glu Ala His Thr Pro Pro Ala Val His  
 545                                   550                      555                      560  
 Ser Asn His Ala Pro Val Thr Gln Ala Arg Glu Gly Asn Leu Pro Leu  
                                  565                      570                      575  
 Leu Ile Ala Pro Ala Leu Ala Ala Val Leu Leu Ala Ala Leu Ala Ala  
                                  580                      585                      590  
 Val Gly Ala Ala Tyr Cys Val Arg Arg Gly Arg Ala Met Ala Ala Ala  
                                  595                      600                      605  
 Ala Gln Asp Lys Gly Gln Val Gly Pro Gly Ala Gly Pro Leu Glu Leu  
                                  610                      615                      620  
 Glu Gly Val Lys Val Pro Leu Glu Pro Gly Pro Lys Ala Thr Glu Gly  
 625                                   630                      635                      640  
 Gly Gly Glu Ala Leu Pro Ser Gly Ser Glu Cys Glu Val Pro Leu Met  
                                  645                      650                      655  
 Gly Phe Pro Gly Pro Gly Leu Gln Ser Pro Leu His Ala Lys Pro Tyr  
                                  660                      665                      670

Ile

<210> 79  
 <211> 696  
 <212> PRT  
 <213> Homo sapiens  
 <400> 79

Met Leu Leu Trp Ile Leu Leu Leu Glu Thr Ser Leu Cys Phe Ala Ala  
 1 5 10 15

Gly Asn Val Thr Gly Asp Val Cys Lys Glu Lys Ile Cys Ser Cys Asn  
 20 25 30

Glu Ile Glu Gly Asp Leu His Val Asp Cys Glu Lys Lys Gly Phe Thr  
 35 40 45

Ser Leu Gln Arg Phe Thr Ala Pro Thr Ser Gln Phe Tyr His Leu Phe  
 50 55 60

Leu His Gly Asn Ser Leu Thr Arg Leu Phe Pro Asn Glu Phe Ala Asn  
 65 70 75 80

Phe Tyr Asn Ala Val Ser Leu His Met Glu Asn Asn Gly Leu His Glu  
 85 90 95

Ile Val Pro Gly Ala Phe Leu Gly Leu Gln Leu Val Lys Arg Leu His  
 100 105 110

Ile Asn Asn Asn Lys Ile Lys Ser Phe Arg Lys Gln Thr Phe Leu Gly  
 115 120 125

Leu Asp Asp Leu Glu Tyr Leu Gln Ala Asp Phe Asn Leu Leu Arg Asp  
 130 135 140

Ile Asp Pro Gly Ala Phe Gln Asp Leu Asn Lys Leu Glu Val Leu Ile  
 145 150 155 160

Leu Asn Asp Asn Leu Ile Ser Thr Leu Pro Ala Asn Val Phe Gln Tyr  
 165 170 175

Val Pro Ile Thr His Leu Asp Leu Arg Gly Asn Arg Leu Lys Thr Leu  
 180 185 190

Pro Tyr Glu Glu Val Leu Glu Gln Ile Pro Gly Ile Ala Glu Ile Leu  
 195 200 205

Leu Glu Asp Asn Pro Trp Asp Cys Thr Cys Asp Leu Leu Ser Leu Lys  
 210 215 220

Glu Trp Leu Glu Asn Ile Pro Lys Asn Ala Leu Ile Gly Arg Val Val  
 225 230 235 240

Cys Glu Ala Pro Thr Arg Leu Gln Gly Lys Asp Leu Asn Glu Thr Thr  
 245 250 255

Glu Gln Asp Leu Cys Pro Leu Lys Asn Arg Val Asp Ser Ser Leu Pro  
 260 265 270

Ala Pro Pro Ala Gln Glu Glu Thr Phe Ala Pro Gly Pro Leu Pro Thr  
 275 280 285

Pro Phe Lys Thr Asn Gly Gln Glu Asp His Ala Thr Pro Gly Ser Ala  
 290 295 300

Pro Asn Gly Gly Thr Lys Ile Pro Gly Asn Trp Gln Ile Lys Ile Arg  
 305 310 315 320

Pro Thr Ala Ala Ile Ala Thr Gly Ser Ser Arg Asn Lys Pro Leu Ala  
 325 330 335

Asn Ser Leu Pro Cys Pro Gly Gly Cys Ser Cys Asp His Ile Pro Gly  
 340 345 350

Ser Gly Leu Lys Met Asn Cys Asn Asn Arg Asn Val Ser Ser Leu Ala  
 355 360 365

Asp Leu Lys Pro Lys Leu Ser Asn Val Gln Glu Leu Phe Leu Arg Asp  
 370 375 380

Asn Lys Ile His Ser Ile Arg Lys Ser His Phe Val Asp Tyr Lys Asn  
 385 390 395 400

Leu Ile Leu Leu Asp Leu Gly Asn Asn Asn Ile Ala Thr Val Glu Asn  
 405 410 415

Asn Thr Phe Lys Asn Leu Leu Asp Leu Arg Trp Leu Tyr Met Asp Ser  
 420 425 430

Asn Tyr Leu Asp Thr Leu Ser Arg Glu Lys Phe Ala Gly Leu Gln Asn  
 435 440 445

Leu Glu Tyr Leu Asn Val Glu Tyr Asn Ala Ile Gln Leu Ile Leu Pro  
 450 455 460

Gly Thr Phe Asn Ala Met Pro Lys Leu Arg Ile Leu Ile Leu Asn Asn  
 465 470 475 480

Asn Leu Leu Arg Ser Leu Pro Val Asp Val Phe Ala Gly Val Ser Leu  
 485 490 495



Ser Lys Leu Ser Leu His Asn Asn Tyr Phe Met Tyr Leu Pro Val Ala  
                   500                                  505                                  510

Gly Val Leu Asp Gln Leu Thr Ser Ile Ile Gln Ile Asp Leu His Gly  
                   515                                  520                                  525

Asn Pro Trp Glu Cys Ser Cys Thr Ile Val Pro Phe Lys Gln Trp Ala  
                   530                                  535                                  540

Glu Arg Leu Gly Ser Glu Val Leu Met Ser Asp Leu Lys Cys Glu Thr  
                   545                                  550                                  555                                  560

Pro Val Asn Phe Phe Arg Lys Asp Phe Met Leu Leu Ser Asn Asp Glu  
                                   565                                  570                                  575

Ile Cys Pro Gln Leu Tyr Ala Arg Ile Ser Pro Thr Leu Thr Ser His  
                                   580                                  585                                  590

Ser Lys Asn Ser Thr Gly Leu Ala Glu Thr Gly Thr His Ser Asn Ser  
                   595                                  600                                  605

Tyr Leu Asp Thr Ser Arg Val Ser Ile Ser Val Leu Val Pro Gly Leu  
                   610                                  615                                  620

Leu Leu Val Phe Val Thr Ser Ala Phe Thr Val Val Gly Met Leu Val  
                   625                                  630                                  635                                  640

Phe Ile Leu Arg Asn Arg Lys Arg Ser Lys Arg Arg Asp Ala Asn Ser  
                                   645                                  650                                  655

Ser Ala Ser Glu Ile Asn Ser Leu Gln Thr Val Cys Asp Ser Ser Tyr  
                                   660                                  665                                  670

Trp His Asn Gly Pro Tyr Asn Ala Asp Gly Ala His Arg Val Tyr Asp  
                   675                                  680                                  685

Cys Gly Ser His Ser Leu Ser Asp  
                   690                                  695

<210> 80  
 <211> 834  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (734)..(767)  
 <223> Xaa can be any naturally occurring amino acid

&lt;400&gt; 80

Met His Thr Cys Cys Pro Pro Val Thr Leu Glu Gln Asp Leu His Arg  
 1 5 10 15

Lys Met His Ser Trp Met Leu Gln Thr Leu Ala Phe Ala Val Thr Ser  
 20 25 30

Leu Val Leu Ser Cys Ala Glu Thr Ile Asp Tyr Tyr Gly Glu Ile Cys  
 35 40 45

Asp Asn Ala Cys Pro Cys Glu Glu Lys Asp Gly Ile Leu Thr Val Ser  
 50 55 60

Cys Glu Asn Arg Gly Ile Ile Ser Leu Ser Glu Ile Ser Pro Pro Arg  
 65 70 75 80

Phe Pro Ile Tyr His Leu Leu Leu Ser Gly Asn Leu Leu Asn Arg Leu  
 85 90 95

Tyr Pro Asn Glu Phe Val Asn Tyr Thr Gly Ala Ser Ile Leu His Leu  
 100 105 110

Gly Ser Asn Val Ile Gln Asp Ile Glu Thr Gly Ala Phe His Gly Leu  
 115 120 125

Arg Gly Leu Arg Arg Leu His Leu Asn Asn Asn Lys Leu Glu Leu Leu  
 130 135 140

Arg Asp Asp Thr Phe Leu Gly Leu Glu Asn Leu Glu Tyr Leu Gln Val  
 145 150 155 160

Asp Tyr Asn Tyr Ile Ser Val Ile Glu Pro Asn Ala Phe Gly Lys Leu  
 165 170 175

His Leu Leu Gln Val Leu Ile Leu Asn Asp Asn Leu Leu Ser Ser Leu  
 180 185 190

Pro Asn Asn Leu Phe Arg Phe Val Pro Leu Thr His Leu Asp Leu Arg  
 195 200 205

Gly Asn Arg Leu Lys Leu Leu Pro Tyr Val Gly Leu Leu Gln His Met  
 210 215 220

Asp Lys Val Val Glu Leu Gln Leu Glu Glu Asn Pro Trp Asn Cys Ser  
 225 230 235 240

Cys Glu Leu Ile Ser Leu Lys Asp Trp Leu Asp Ser Ile Ser Tyr Ser  
 245 250 255

Ala Leu Val Gly Asp Val Val Cys Glu Thr Pro Phe Arg Leu His Gly  
 260 265 270

Arg Asp Leu Asp Glu Val Ser Lys Gln Glu Leu Cys Pro Arg Arg Leu  
 275 280 285

Ile Ser Asp Tyr Glu Met Arg Pro Gln Thr Pro Leu Ser Thr Thr Gly  
 290 295 300

Tyr Leu His Thr Thr Pro Ala Ser Val Asn Ser Val Ala Thr Ser Ser  
 305 310 315 320

Ser Ala Val Tyr Lys Pro Pro Leu Lys Pro Pro Lys Gly Thr Arg Gln  
 325 330 335

Pro Asn Lys Pro Arg Val Arg Pro Thr Ser Arg Gln Pro Ser Lys Asp  
 340 345 350

Leu Gly Tyr Ser Asn Tyr Gly Pro Ser Ile Ala Tyr Gln Thr Lys Ser  
 355 360 365

Pro Val Pro Leu Glu Cys Pro Thr Ala Cys Ser Cys Asn Leu Gln Ile  
 370 375 380

Ser Asp Leu Gly Leu Asn Val Asn Cys Gln Glu Arg Lys Ile Glu Ser  
 385 390 395 400

Ile Ala Glu Leu Gln Pro Lys Pro Tyr Asn Pro Lys Lys Met Tyr Leu  
 405 410 415

Thr Glu Asn Tyr Ile Ala Val Val Arg Arg Thr Asp Phe Leu Glu Ala  
 420 425 430

Thr Gly Leu Asp Leu Leu His Leu Gly Asn Asn Arg Ile Ser Met Ile  
 435 440 445

Gln Asp Arg Ala Phe Gly Asp Leu Thr Asn Leu Arg Arg Leu Tyr Leu  
 450 455 460

Asn Gly Asn Arg Ile Glu Arg Leu Ser Pro Glu Leu Phe Tyr Gly Leu  
 465 470 475 480

Gln Ser Leu Gln Tyr Leu Phe Leu Gln Tyr Asn Leu Ile Arg Glu Ile

485	490	495
Gln Ser Gly Thr Phe Asp Pro Val	Pro Asn Leu Gln Leu Leu Phe Leu	
500	505	510
Asn Asn Asn Leu Leu Gln Ala Met	Pro Ser Gly Val Phe Ser Gly Leu	
515	520	525
Thr Leu Leu Arg Leu Asn Leu Arg	Ser Asn His Phe Thr Ser Leu Pro	
530	535	540
Val Ser Gly Val Leu Asp Gln Leu Lys	Ser Leu Ile Gln Ile Asp Leu	
545	550	555
His Asp Asn Pro Trp Asp Cys Thr	Cys Asp Ile Val Gly Met Lys Leu	
565	570	575
Trp Val Glu Gln Leu Lys Val Gly	Val Leu Val Asp Glu Val Ile Cys	
580	585	590
Lys Ala Pro Lys Lys Phe Ala Glu	Thr Asp Met Arg Ser Ile Lys Ser	
595	600	605
Glu Leu Leu Cys Pro Asp Tyr Ser	Asp Val Val Val Ser Thr Pro Thr	
610	615	620
Pro Ser Ser Ile Gln Val Pro Ala	Arg Thr Ser Ala Val Thr Pro Ala	
625	630	635
Val Arg Leu Asn Ser Thr Gly Ala	Pro Ala Ser Leu Gly Ala Gly Gly	
645	650	655
Gly Ala Ser Ser Val Pro Leu Ser	Val Leu Ile Leu Ser Leu Leu Leu	
660	665	670
Val Phe Ile Met Ser Val Phe Val	Ala Ala Gly Leu Phe Val Leu Val	
675	680	685
Met Lys Arg Arg Lys Lys Asn Gln	Ser Asp His Thr Ser Thr Asn Asn	
690	695	700
Ser Asp Val Ser Ser Phe Asn Met	Gln Tyr Ser Val Tyr Gly Gly Gly	
705	710	715
Gly Gly Thr Gly Gly His Pro His	Ala His Val His Tyr Xaa Xaa Xaa	
725	730	735

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
                   740                                  745                                  750

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr  
                   755                                  760                                  765

Ala Ala Ala Pro Ala Ala Ala Ala Ala Ala Ala Arg Gly Gly Gly Glu  
                   770                                  775                                  780

Ala Gly Lys Pro Pro Leu Ala Glu Pro Arg Leu Gln Arg Gln His His  
                   785                                  790                                  795                                  800

Arg Ala Pro Gly Gly Pro Ala Val Ala Gly Ala Gly Arg Arg Pro Leu  
                   805                                  810                                  815

Leu Gln Gly His Phe Arg Thr Arg Gln Thr Leu Leu His His Pro Arg  
                   820                                  825                                  830

Arg Gln

<210> 81  
 <211> 853  
 <212> PRT  
 <213> Homo sapiens

<400> 81

Tyr Phe Ser Leu Phe Arg Ser Ile Gln Leu Phe Ala Asp Cys Lys Lys  
   1                  5                                  10                                  15

Met Phe Leu Trp Leu Phe Leu Ile Leu Ser Ala Leu Ile Ser Ser Thr  
                   20                                  25                                  30

Asn Ala Asp Ser Asp Ile Ser Val Glu Ile Cys Asn Val Cys Ser Cys  
                   35                                  40                                  45

Val Ser Val Glu Asn Val Leu Tyr Val Asn Cys Glu Lys Val Ser Val  
                   50                                  55                                  60

Tyr Arg Pro Asn Gln Leu Lys Pro Pro Trp Ser Asn Phe Tyr His Leu  
   65                                  70                                  75                                  80

Asn Phe Gln Asn Asn Phe Leu Asn Ile Leu Tyr Pro Asn Thr Phe Leu  
                   85                                  90                                  95

Asn Phe Ser His Ala Val Ser Leu His Leu Gly Asn Asn Lys Leu Gln  
                   100                                  105                                  110

Asn Ile Glu Gly Gly Ala Phe Leu Gly Leu Ser Ala Leu Lys Gln Leu  
 115 120 125

His Leu Asn Asn Asn Glu Leu Lys Ile Leu Arg Ala Asp Thr Phe Leu  
 130 135 140

Gly Ile Glu Asn Leu Glu Tyr Leu Gln Ala Asp Tyr Asn Leu Ile Lys  
 145 150 155 160

Tyr Ile Glu Arg Gly Ala Phe Asn Lys Leu His Lys Leu Lys Val Leu  
 165 170 175

Ile Leu Asn Asp Asn Leu Ile Ser Phe Leu Pro Asp Asn Ile Phe Arg  
 180 185 190

Phe Ala Ser Leu Thr His Leu Asp Ile Arg Gly Asn Arg Ile Gln Lys  
 195 200 205

Leu Pro Tyr Ile Gly Val Leu Glu His Ile Gly Arg Val Val Glu Leu  
 210 215 220

Gln Leu Glu Asp Asn Pro Trp Asn Cys Ser Cys Asp Leu Leu Pro Leu  
 225 230 235 240

Lys Ala Trp Leu Glu Asn Met Pro Tyr Asn Ile Tyr Ile Gly Glu Ala  
 245 250 255

Ile Cys Glu Thr Pro Ser Asp Leu Tyr Gly Arg Leu Leu Lys Glu Thr  
 260 265 270

Asn Lys Gln Glu Leu Cys Pro Met Gly Thr Gly Ser Asp Phe Asp Val  
 275 280 285

Arg Ile Leu Pro Pro Ser Gln Leu Glu Asn Gly Tyr Thr Thr Pro Asn  
 290 295 300

Gly His Thr Thr Gln Thr Ser Leu His Arg Leu Val Thr Lys Pro Pro  
 305 310 315 320

Lys Thr Thr Asn Pro Ser Lys Ile Ser Gly Ile Val Ala Gly Lys Ala  
 325 330 335

Leu Ser Asn Arg Asn Leu Ser Gln Ile Val Ser Tyr Gln Thr Arg Val  
 340 345 350

Pro Pro Leu Thr Pro Cys Pro Ala Pro Cys Phe Cys Lys Thr His Pro  
 355 360 365

Ser Asp Leu Gly Leu Ser Val Asn Cys Gln Glu Lys Asn Ile Gln Ser  
 370 375 380

Met Ser Glu Leu Ile Pro Lys Pro Leu Asn Ala Lys Lys Leu His Val  
 385 390 395 400

Asn Gly Asn Ser Ile Lys Asp Val Asp Val Ser Asp Phe Thr Asp Phe  
 405 410 415

Glu Gly Leu Asp Leu Leu His Leu Gly Ser Asn Gln Ile Thr Val Ile  
 420 425 430

Lys Gly Asp Val Phe His Asn Leu Thr Asn Leu Arg Arg Leu Tyr Leu  
 435 440 445

Asn Gly Asn Gln Ile Glu Arg Leu Tyr Pro Glu Ile Phe Ser Gly Leu  
 450 455 460

His Asn Leu Gln Tyr Leu Tyr Leu Glu Tyr Asn Leu Ile Lys Glu Ile  
 465 470 475 480

Ser Ala Gly Thr Phe Asp Ser Met Pro Asn Leu Gln Leu Leu Tyr Leu  
 485 490 495

Asn Asn Asn Leu Leu Lys Ser Leu Pro Val Tyr Ile Phe Ser Gly Ala  
 500 505 510

Pro Leu Ala Arg Leu Asn Leu Arg Asn Asn Lys Phe Met Tyr Leu Pro  
 515 520 525

Val Ser Gly Val Leu Asp Gln Leu Gln Ser Leu Thr Gln Ile Asp Leu  
 530 535 540

Glu Gly Asn Pro Trp Asp Cys Thr Cys Asp Leu Val Ala Leu Lys Leu  
 545 550 555 560

Trp Val Glu Lys Leu Ser Asp Gly Ile Val Val Lys Glu Leu Lys Cys  
 565 570 575

Glu Thr Pro Val Gln Phe Ala Asn Ile Glu Leu Lys Ser Leu Lys Asn  
 580 585 590

Glu Ile Leu Cys Pro Lys Leu Leu Asn Lys Pro Ser Ala Pro Phe Thr  
 595 600 605

Ser Pro Ala Pro Ala Ile Thr Phe Thr Thr Pro Leu Gly Pro Ile Arg  
610 615 620

Ser Pro Pro Gly Gly Pro Val Pro Leu Ser Ile Leu Ile Leu Ser Ile  
625 630 635 640

Leu Val Val Leu Ile Leu Thr Val Phe Val Ala Phe Cys Leu Leu Val  
645 650 655

Phe Val Leu Arg Arg Asn Lys Lys Pro Thr Val Lys His Glu Gly Leu  
660 665 670

Gly Asn Pro Asp Cys Gly Ser Met Gln Leu Gln Leu Arg Lys His Asp  
675 680 685

His Lys Thr Asn Lys Lys Asp Gly Leu Ser Thr Glu Ala Phe Ile Pro  
690 695 700

Gln Thr Ile Glu Gln Met Ser Lys Ser His Thr Cys Gly Leu Lys Glu  
705 710 715 720

Ser Glu Thr Gly Phe Met Phe Ser Asp Pro Pro Gly Gln Lys Val Val  
725 730 735

Met Arg Asn Val Ala Asp Lys Glu Lys Asp Leu Leu His Val Asp Thr  
740 745 750

Arg Lys Arg Leu Ser Thr Ile Asp Glu Leu Asp Glu Leu Phe Pro Ser  
755 760 765

Arg Asp Ser Asn Val Phe Ile Gln Asn Phe Leu Glu Ser Lys Lys Glu  
770 775 780

Tyr Asn Ser Ile Gly Val Ser Gly Phe Glu Ile Arg Tyr Pro Glu Lys  
785 790 795 800

Gln Pro Asp Lys Lys Ser Lys Lys Ser Leu Ile Gly Gly Asn His Ser  
805 810 815

Lys Ile Val Val Glu Gln Arg Lys Ser Glu Tyr Phe Glu Leu Lys Ala  
820 825 830

Lys Leu Gln Ser Ser Pro Asp Tyr Leu Gln Val Leu Glu Glu Gln Thr  
835 840 845



Ala Leu Asn Lys Ile  
850

<210> 82  
<211> 977  
<212> PRT  
<213> Homo sapiens

<400> 82

Met Lys Pro Ser Ile Ala Glu Met Leu His Arg Gly Arg Met Leu Trp  
1 5 10 15

Ile Ile Leu Leu Ser Thr Ile Ala Leu Gly Trp Thr Thr Pro Ile Pro  
20 25 30

Leu Ile Glu Asp Ser Glu Glu Ile Asp Glu Pro Cys Phe Asp Pro Cys  
35 40 45

Tyr Cys Glu Val Lys Glu Ser Leu Phe His Ile His Cys Asp Ser Lys  
50 55 60

Gly Phe Thr Asn Ile Ser Gln Ile Thr Glu Phe Trp Ser Arg Pro Phe  
65 70 75 80

Lys Leu Tyr Leu Gln Arg Asn Ser Met Arg Lys Leu Tyr Thr Asn Ser  
85 90 95

Phe Leu His Leu Asn Asn Ala Val Ser Ile Asn Leu Gly Asn Asn Ala  
100 105 110

Leu Gln Asp Ile Gln Thr Gly Ala Phe Asn Gly Leu Lys Ile Leu Lys  
115 120 125

Arg Leu Tyr Leu His Glu Asn Lys Leu Asp Val Phe Arg Asn Asp Thr  
130 135 140

Phe Leu Gly Leu Glu Ser Leu Glu Tyr Leu Gln Ala Asp Tyr Asn Val  
145 150 155 160

Ile Lys Arg Ile Glu Ser Gly Ala Phe Arg Asn Leu Ser Lys Leu Arg  
165 170 175

Val Leu Ile Leu Asn Asp Asn Leu Ile Pro Met Leu Pro Thr Asn Leu  
180 185 190

Phe Lys Ala Val Ser Leu Thr His Leu Asp Leu Arg Gly Asn Arg Leu  
195 200 205

Lys Val Leu Phe Tyr Arg Gly Met Leu Asp His Ile Gly Arg Ser Leu  
 210 215 220

Met Glu Leu Gln Leu Glu Glu Asn Pro Trp Asn Cys Thr Cys Glu Ile  
 225 230 235 240

Val Gln Leu Lys Ser Trp Leu Glu Arg Ile Pro Tyr Thr Ala Leu Val  
 245 250 255

Gly Asp Ile Thr Cys Glu Thr Pro Phe His Phe His Gly Lys Asp Leu  
 260 265 270

Arg Glu Ile Arg Lys Thr Glu Leu Cys Pro Leu Leu Ser Asp Ser Glu  
 275 280 285

Val Glu Ala Ser Leu Gly Ile Pro His Ser Ser Ser Ser Lys Glu Asn  
 290 295 300

Ala Trp Pro Thr Lys Pro Ser Ser Met Leu Ser Ser Val His Phe Thr  
 305 310 315 320

Ala Ser Ser Val Glu Tyr Lys Ser Ser Asn Lys Gln Pro Lys Pro Thr  
 325 330 335

Lys Gln Pro Arg Thr Pro Arg Pro Pro Ser Thr Ser Gln Ala Leu Tyr  
 340 345 350

Pro Gly Pro Asn Gln Pro Pro Ile Ala Pro Tyr Gln Thr Arg Pro Pro  
 355 360 365

Ile Pro Ile Ile Cys Pro Thr Gly Cys Thr Cys Asn Leu His Ile Asn  
 370 375 380

Asp Leu Gly Leu Thr Val Asn Cys Lys Glu Arg Gly Phe Asn Asn Ile  
 385 390 395 400

Ser Glu Leu Leu Pro Arg Pro Leu Asn Ala Lys Lys Leu Tyr Leu Ser  
 405 410 415

Ser Asn Leu Ile Gln Lys Ile Tyr Arg Ser Asp Phe Trp Asn Phe Ser  
 420 425 430

Ser Leu Asp Leu Leu His Leu Gly Asn Asn Arg Ile Ser Tyr Val Gln  
 435 440 445

Asp Gly Ala Phe Ile Asn Leu Pro Asn Leu Lys Ser Leu Phe Leu Asn

450	455	460
Gly Asn Asp Ile Glu Lys Leu Thr Pro Gly Met Phe Arg Gly Leu Gln		
465	470	475 480
Ser Leu His Tyr Leu Tyr Phe Glu Phe Asn Val Ile Arg Glu Ile Gln		
	485	490 495
Pro Ala Ala Phe Ser Leu Met Pro Asn Leu Lys Leu Leu Phe Leu Asn		
	500	505 510
Asn Asn Leu Leu Arg Thr Leu Pro Thr Asp Ala Phe Ala Gly Thr Ser		
	515	520 525
Leu Ala Arg Leu Asn Leu Arg Lys Asn Tyr Phe Leu Tyr Leu Pro Val		
	530	535 540
Ala Gly Val Leu Glu His Leu Asn Ala Ile Val Gln Ile Asp Leu Asn		
	545	550 555 560
Glu Asn Pro Trp Asp Cys Thr Cys Asp Leu Val Pro Phe Lys Gln Trp		
	565	570 575
Ile Glu Thr Ile Ser Ser Val Ser Val Val Gly Asp Val Leu Cys Arg		
	580	585 590
Ser Pro Glu Asn Leu Thr His Arg Asp Val Arg Thr Ile Glu Leu Glu		
	595	600 605
Val Leu Cys Pro Glu Met Leu His Val Ala Pro Ala Gly Glu Ser Pro		
	610	615 620
Ala Gln Pro Gly Asp Ser His Leu Ile Gly Ala Pro Thr Ser Ala Ser		
	625	630 635 640
Pro Tyr Glu Phe Ser Pro Pro Gly Gly Pro Val Pro Leu Ser Val Leu		
	645	650 655
Ile Leu Ser Leu Leu Val Leu Phe Phe Ser Ala Val Phe Val Ala Ala		
	660	665 670
Gly Leu Phe Ala Tyr Val Leu Arg Arg Arg Arg Lys Lys Leu Pro Phe		
	675	680 685
Arg Ser Lys Arg Gln Glu Gly Val Asp Leu Thr Gly Ile Gln Met Gln		
	690	695 700

Cys His Arg Leu Phe Glu Asp Gly Gly Gly Gly Gly Gly Ser Gly  
705 710 715 720

Gly Gly Gly Arg Pro Thr Leu Ser Ser Pro Glu Lys Ala Pro Pro Val  
725 730 735

Gly His Val Tyr Glu Tyr Ile Pro His Pro Val Thr Gln Met Cys Asn  
740 745 750

Asn Pro Ile Tyr Lys Pro Arg Glu Glu Glu Val Ala Val Ser Ser  
755 760 765

Ala Gln Glu Ala Gly Ser Ala Glu Arg Gly Gly Pro Gly Thr Gln Pro  
770 775 780

Pro Gly Met Gly Glu Ala Leu Leu Gly Ser Glu Gln Phe Ala Glu Thr  
785 790 795 800

Pro Lys Glu Asn His Ser Asn Tyr Arg Thr Leu Leu Glu Lys Glu Lys  
805 810 815

Glu Trp Ala Leu Ala Val Ser Ser Ser Gln Leu Asn Thr Ile Val Thr  
820 825 830

Val Asn His His His Pro His His Pro Ala Val Gly Gly Val Ser Gly  
835 840 845

Val Val Gly Gly Thr Gly Gly Asp Leu Ala Gly Phe Arg His His Glu  
850 855 860

Lys Asn Gly Gly Val Val Leu Phe Pro Pro Gly Gly Gly Cys Gly Ser  
865 870 875 880

Gly Ser Met Leu Leu Asp Arg Glu Arg Pro Gln Pro Ala Pro Cys Thr  
885 890 895

Val Gly Phe Val Asp Cys Leu Tyr Gly Thr Val Pro Lys Leu Lys Glu  
900 905 910

Leu His Val His Pro Pro Gly Met Gln Tyr Pro Asp Leu Gln Gln Asp  
915 920 925

Ala Arg Leu Lys Glu Thr Leu Leu Phe Ser Ala Glu Lys Gly Phe Thr  
930 935 940

Asp His Gln Thr Gln Lys Ser Asp Tyr Leu Glu Leu Arg Ala Lys Leu

945					950					955					960
Gln	Thr	Lys	Pro	Asp	Tyr	Leu	Glu	Val	Leu	Glu	Lys	Thr	Thr	Tyr	Arg
				965					970					975	

Phe

```
<210>      83
<211>      921
<212>      PRT
<213>      Homo sapiens

<400>      83
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Met Ala Asp Asp Asp Val Leu Phe Glu Asp Val Tyr Glu Leu Cys Glu  
1 5 10 15

Val Ile Gly Lys Gly Pro Phe Ser Val Val Arg Arg Cys Ile Asn Arg  
20 25 30

Glu Thr Gly Gln Gln Phe Ala Val Lys Ile Val Asp Val Ala Lys Phe  
35 40 45

Thr Ser Ser Pro Gly Leu Ser Thr Glu Asp Leu Lys Arg Glu Ala Ser  
50 55 60

Ile Cys His Met Leu Lys His Pro His Ile Val Glu Leu Leu Glu Thr  
65 70 75 80

Tyr Ser Ser Asp Gly Met Leu Tyr Met Val Phe Glu Phe Met Asp Gly  
85 90 95

Ala Asp Leu Cys Phe Glu Ile Val Lys Arg Ala Asp Ala Gly Phe Val  
100 105 110

Tyr Ser Glu Ala Val Ala Ser His Tyr Met Arg Gln Ile Leu Glu Ala  
115 120 125

Leu Arg Tyr Cys His Asp Asn Asn Ile Ile His Arg Asp Val Lys Pro  
130 135 140

His	Cys	Val	Leu	Leu	Ala	Ser	Lys	Glu	Asn	Ser	Ala	Pro	Val	Lys	Leu
145					150					155					160

Gly Gly Phe Gly Val Ala Ile Gln Leu Gly Glu Ser Gly Leu Val Ala  
165 170 175

Gly Gly Arg Val Gly Thr Pro His Phe Met Ala Pro Glu Val Val Lys  
 180 185 190

Arg Glu Pro Tyr Gly Lys Pro Val Asp Val Trp Gly Cys Gly Val Ile  
 195 200 205

Leu Phe Ile Leu Leu Ser Gly Cys Leu Pro Phe Tyr Gly Thr Lys Glu  
 210 215 220

Arg Leu Phe Glu Gly Ile Ile Lys Gly Lys Tyr Lys Met Asn Pro Arg  
 225 230 235 240

Gln Trp Ser His Ile Ser Glu Ser Ala Lys Asp Leu Val Arg Arg Met  
 245 250 255

Leu Met Leu Asp Pro Ala Glu Arg Ile Thr Val Tyr Glu Ala Leu Asn  
 260 265 270

His Pro Trp Leu Lys Glu Arg Asp Arg Tyr Ala Tyr Lys Ile His Leu  
 275 280 285

Pro Glu Thr Val Glu Gln Leu Arg Lys Phe Asn Ala Arg Arg Lys Leu  
 290 295 300

Lys Gly Ala Val Leu Ala Ala Val Ser Ser His Lys Phe Asn Ser Phe  
 305 310 315 320

Tyr Gly Asp Pro Pro Glu Glu Leu Pro Asp Phe Ser Glu Asp Pro Thr  
 325 330 335

Ser Ser Gly Leu Leu Ala Ala Glu Arg Ala Val Ser Gln Val Leu Asp  
 340 345 350

Ser Leu Glu Glu Ile His Ala Leu Thr Asp Cys Ser Glu Lys Asp Leu  
 355 360 365

Asp Phe Leu His Ser Val Phe Gln Asp Gln His Leu His Thr Leu Leu  
 370 375 380

Asp Leu Tyr Asp Lys Ile Asn Thr Lys Ser Ser Pro Gln Ile Arg Asn  
 385 390 395 400

Pro Pro Ser Asp Ala Val Gln Arg Ala Lys Glu Val Leu Glu Glu Ile  
 405 410 415

Ser Cys Tyr Pro Glu Asn Asn Asp Ala Lys Glu Leu Lys Arg Ile Leu  
 420 425 430

Thr Gln Pro His Phe Met Ala Leu Leu Gln Thr His Asp Val Val Ala  
 435 440 445

His Glu Val Tyr Ser Asp Glu Ala Leu Arg Val Thr Pro Pro Pro Thr  
 450 455 460

Ser Pro Tyr Leu Asn Gly Asp Ser Pro Glu Ser Ala Asn Gly Gly Met  
 465 470 475 480

Asp Met Glu Asn Val Thr Arg Val Arg Leu Val Gln Phe Gln Lys Asn  
 485 490 495

Thr Asp Glu Pro Met Gly Ile Thr Leu Lys Met Asn Glu Leu Asn His  
 500 505 510

Cys Ile Val Ala Arg Ile Met His Gly Gly Met Ile His Arg Gln Gly  
 515 520 525

Thr Leu His Val Gly Asp Glu Ile Arg Glu Ile Asn Gly Ile Ser Val  
 530 535 540

Ala Asn Gln Thr Val Glu Gln Leu Gln Lys Met Leu Arg Glu Met Arg  
 545 550 555 560

Gly Ser Ile Thr Phe Lys Ile Val Pro Ser Tyr Arg Thr Gln Ser Ser  
 565 570 575

Ser Cys Glu Arg Asp Ser Pro Ser Thr Ser Arg Gln Ser Pro Ala Asn  
 580 585 590

Gly His Ser Ser Thr Asn Asn Ser Val Ser Asp Leu Pro Ser Thr Thr  
 595 600 605

Gln Pro Lys Gly Arg Gln Ile Tyr Val Arg Ala Gln Phe Glu Tyr Asp  
 610 615 620

Pro Ala Lys Asp Asp Leu Ile Pro Cys Lys Glu Ala Gly Ile Arg Phe  
 625 630 635 640

Arg Val Gly Asp Ile Ile Gln Ile Ile Ser Lys Asp Asp His Asn Trp  
 645 650 655

Trp Gln Gly Lys Leu Glu Asn Ser Lys Asn Gly Thr Ala Gly Leu Ile  
 660 665 670

Pro Ser Ser Glu Leu Gln Glu Trp Arg Val Ala Cys Ile Ala Met Glu  
675 680 685

Lys Thr Lys Gln Glu Gln Gln Ala Ser Cys Thr Trp Phe Gly Lys Lys  
690 695 700

Lys Lys Gln Tyr Lys Asp Lys Tyr Leu Ala Lys His Asn Ala Asp Leu  
705 710 715 720

Val Thr Tyr Glu Glu Val Val Lys Leu Pro Ala Phe Lys Arg Lys Thr  
725 730 735

Leu Val Leu Leu Gly Ala His Gly Val Gly Arg Arg His Ile Lys Asn  
740 745 750

Thr Leu Ile Thr Lys His Pro Asp Arg Phe Ala Tyr Pro Ile Pro His  
755 760 765

Thr Thr Arg Pro Pro Lys Arg Asp Glu Glu Asn Gly Lys Asn Tyr Tyr  
770 775 780

Phe Val Ser His Asp Gln Met Met Gln Asp Ile Ser Asn Asn Glu Tyr  
785 790 795 800

Leu Glu Tyr Gly Ser His Glu Asp Ala Met Tyr Gly Thr Lys Leu Glu  
805 810 815

Thr Ile Arg Lys Ile His Glu Gln Gly Leu Ile Ala Ile Leu Asp Val  
820 825 830

Glu Pro Gln Ala Leu Lys Val Leu Arg Thr Ala Glu Phe Ala Pro Phe  
835 840 845

Val Val Phe Ile Ala Ala Pro Thr Ile Thr Pro Gly Leu Asn Glu Asp  
850 855 860

Glu Ser Leu Gln Arg Leu Gln Lys Glu Ser Asp Ile Leu Gln Arg Thr  
865 870 875 880

Tyr Ala His Tyr Phe Asp Leu Thr Ile Ile Asn Asn Glu Ile Asp Glu  
885 890 895

Thr Ile Arg His Leu Glu Glu Ala Val Glu Leu Val Cys Thr Ala Pro  
900 905 910

Gln Trp Val Pro Val Ser Trp Val Tyr  
915 920



<210> 84  
 <211> 837  
 <212> PRT  
 <213> Homo sapiens

<400> 84

Met Asn His Leu Glu Gly Ser Ala Glu Val Glu Val Thr Asp Glu Ala  
 1 5 10 15

Ala Gly Gly Glu Val Asn Glu Ser Val Glu Ala Asp Leu Glu His Pro  
 20 25 30

Glu Val Glu Glu Glu Gln Gln Gln Pro Pro Gln Gln Gln His Tyr Val  
 35 40 45

Gly Arg His Gln Arg Gly Arg Ala Leu Glu Asp Leu Arg Ala Gln Leu  
 50 55 60

Gly Gln Glu Glu Glu Glu Arg Gly Glu Cys Leu Ala Arg Ser Ala Ser  
 65 70 75 80

Thr Glu Ser Gly Phe His Asn His Thr Asp Thr Ala Glu Gly Asp Val  
 85 90 95

Ile Ala Ala Ala Arg Asp Gly Tyr Asp Ala Glu Arg Ala Gln Asp Pro  
 100 105 110

Glu Asp Glu Ser Ala Tyr Ala Val Gln Tyr Arg Pro Glu Ala Glu Glu  
 115 120 125

Tyr Thr Glu Gln Ala Glu Ala Glu His Ala Glu Ala Thr His Arg Arg  
 130 135 140

Ala Leu Pro Asn His Leu His Phe His Ser Leu Glu His Glu Glu Ala  
 145 150 155 160

Met Asn Ala Ala Tyr Ser Gly Tyr Val Tyr Thr His Arg Leu Phe His  
 165 170 175

Arg Gly Glu Asp Glu Pro Tyr Ser Glu Pro Tyr Ala Asp Tyr Gly Gly  
 180 185 190

Leu Gln Glu His Val Tyr Glu Glu Ile Gly Asp Ala Pro Glu Leu His  
 195 200 205

Ala Arg Asp Gly Leu Arg Leu Tyr Glu Gln Glu Arg Asp Glu Ala Ala

210	215	220	
Ala Tyr Arg Gln Glu Ala Leu Gly Ala Arg Leu His His Tyr Asp Glu			
225	230	235	240
Arg Ser Asp Gly Glu Ser Asp Ser Pro Glu Lys Glu Ala Glu Phe Ala			
	245	250	255
Pro Tyr Pro Arg Met Asp Ser Tyr Glu Gln Glu Glu Asp Ile Asp Gln			
	260	265	270
Ile Val Ala Glu Val Lys Gln Ser Met Ser Ser Gln Ser Leu Asp Lys			
	275	280	285
Ala Ala Glu Asp Met Pro Glu Ala Glu Gln Asp Leu Glu Arg Pro Pro			
	290	295	300
Thr Pro Ala Gly Gly Arg Pro Asp Ser Pro Gly Leu Gln Ala Pro Ala			
305	310	315	320
Gly Gln Gln Arg Ala Val Gly Pro Ala Gly Gly Gly Glu Ala Gly Gln			
	325	330	335
Arg Tyr Ser Lys Glu Lys Arg Asp Ala Ile Ser Leu Ala Ile Lys Asp			
	340	345	350
Ile Lys Glu Ala Ile Glu Glu Val Lys Thr Arg Thr Ile Arg Ser Pro			
	355	360	365
Tyr Thr Pro Asp Glu Pro Lys Glu Pro Ile Trp Val Met Arg Gln Asp			
	370	375	380
Ile Ser Pro Thr Arg Asp Cys Asp Asp Gln Arg Pro Met Asp Gly Asp			
385	390	395	400
Ser Pro Ser Pro Gly Ser Ser Ser Pro Leu Gly Ala Glu Ser Ser Ser			
	405	410	415
Thr Ser Leu His Pro Ser Asp Pro Val Glu Val Pro Ile Asn Lys Glu			
	420	425	430
Ser Arg Lys Ser Leu Ala Ser Phe Pro Thr Tyr Val Glu Val Pro Gly			
	435	440	445
Pro Cys Asp Pro Glu Asp Leu Ile Asp Gly Ile Ile Phe Ala Ala Asn			
	450	455	460

Tyr Leu Gly Ser Thr Gln Leu Leu Ser Asp Lys Thr Pro Ser Lys Asn  
 465 470 475 480

Val Arg Met Met Gln Ala Gln Glu Ala Val Ser Arg Ile Lys Met Ala  
 485 490 495

Gln Lys Leu Ala Lys Ser Arg Lys Lys Ala Pro Glu Gly Glu Ser Gln  
 500 505 510

Pro Met Thr Glu Val Asp Leu Phe Ile Leu Thr Gln Arg Ile Lys Val  
 515 520 525

Leu Asn Ala Asp Thr Gln Glu Thr Met Met Asp His Pro Leu Arg Thr  
 530 535 540

Ile Ser Tyr Ile Ala Asp Ile Gly Asn Ile Val Val Leu Met Ala Arg  
 545 550 555 560

Arg Arg Ile Pro Arg Ser Asn Ser Gln Glu Asn Val Glu Ala Ser His  
 565 570 575

Pro Ser Gln Asp Gly Lys Arg Gln Tyr Lys Met Ile Cys His Val Phe  
 580 585 590

Glu Ser Glu Asp Ala Gln Leu Ile Ala Gln Ser Ile Gly Gln Ala Phe  
 595 600 605

Ser Val Ala Tyr Gln Glu Phe Leu Arg Ala Asn Gly Ile Asn Pro Glu  
 610 615 620

Asp Leu Ser Gln Lys Glu Tyr Ser Asp Leu Leu Asn Thr Gln Asp Met  
 625 630 635 640

Tyr Asn Asp Asp Leu Ile His Phe Ser Lys Ser Glu Asn Cys Lys Asp  
 645 650 655

Val Phe Ile Glu Lys Gln Lys Gly Glu Ile Leu Gly Val Val Ile Val  
 660 665 670

Glu Ser Gly Trp Gly Ser Ile Leu Pro Thr Val Ile Ile Ala Asn Met  
 675 680 685

Met His Gly Gly Pro Ala Glu Lys Ser Gly Lys Leu Asn Ile Gly Asp  
 690 695 700

Gln Ile Met Ser Ile Asn Gly Thr Ser Leu Val Gly Leu Pro Leu Ser

705                      710                      715                      720  
 Thr Cys Gln Ser Ile Ile Lys Gly Leu Glu Asn Gln Ser Arg Val Lys  
                                  725                      730                      735  
 Leu Asn Ile Val Arg Cys Pro Pro Val Thr Thr Val Leu Ile Arg Arg  
                                  740                      745                      750  
 Pro Asp Leu Arg Tyr Gln Leu Gly Phe Ser Val Gln Asn Gly Ile Ile  
                                  755                      760                      765  
 Cys Ser Leu Met Arg Gly Gly Ile Ala Glu Arg Gly Gly Val Arg Val  
                                  770                      775                      780  
 Gly His Arg Ile Ile Glu Ile Asn Gly Gln Ser Val Val Ala Thr Pro  
                                  785                      790                      795                      800  
 His Glu Lys Ile Val His Ile Leu Ser Asn Ala Val Gly Glu Ile His  
                                  805                      810                      815  
 Met Lys Thr Met Pro Ala Ala Met Tyr Arg Leu Leu Thr Ala Gln Glu  
                                  820                      825                      830  
 Gln Pro Val Tyr Ile  
                                  835  
  
 <210> 85  
 <211> 197  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 85  
 Met Ala Ala Leu Gly Glu Pro Val Arg Leu Glu Arg Asp Ile Cys Arg  
 1                      5                      10                      15  
 Ala Ile Glu Leu Leu Glu Lys Leu Gln Arg Ser Gly Glu Val Pro Pro  
                                  20                      25                      30  
 Gln Lys Leu Gln Ala Leu Gln Arg Val Leu Gln Ser Glu Phe Cys Asn  
                                  35                      40                      45  
 Ala Val Arg Glu Val Tyr Glu His Val Tyr Glu Thr Val Asp Ile Ser  
                                  50                      55                      60  
 Ser Ser Pro Glu Val Arg Ala Asn Ala Thr Ala Lys Ala Thr Val Ala  
                                  65                      70                      75                      80

Ala Phe Ala Ala Ser Glu Gly His Ser His Pro Arg Val Val Glu Leu  
85 90 95

Pro Lys Thr Glu Glu Gly Leu Gly Phe Asn Ile Met Gly Gly Lys Glu  
100 105 110

Gln Asn Ser Pro Ile Tyr Ile Ser Arg Ile Ile Pro Gly Gly Ile Ala  
115 120 125

Asp Arg His Gly Gly Leu Lys Arg Gly Asp Gln Leu Leu Ser Val Asn  
130 135 140

Gly Val Ser Val Glu Gly Glu His His Glu Lys Ala Val Glu Leu Leu  
145 150 155 160

Lys Ala Ala Gln Gly Lys Val Lys Leu Val Val Arg Tyr Thr Pro Lys  
165 170 175

Val Leu Glu Glu Met Glu Ser Arg Phe Glu Lys Met Arg Ser Ala Lys  
180 185 190

Arg Arg Gln Gln Thr  
195

<210> 86  
<211> 744  
<212> PRT  
<213> Homo sapiens

<400> 86

Met Ala Lys Arg Glu Asp Ser Pro Gly Pro Glu Val Gln Pro Met Asp  
1 5 10 15

Lys Gln Phe Leu Val Cys Ser Ile Cys Leu Asp Arg Tyr Gln Cys Pro  
20 25 30

Lys Val Leu Pro Cys Leu His Thr Phe Cys Glu Arg Cys Leu Gln Asn  
35 40 45

Tyr Ile Pro Ala Gln Ser Leu Thr Leu Ser Cys Pro Val Cys Arg Gln  
50 55 60

Thr Ser Ile Leu Pro Glu Gln Gly Val Ser Ala Leu Gln Asn Asn Phe  
65 70 75 80

Phe Ile Ser Ser Leu Met Glu Ala Met Gln Gln Ala Pro Asp Gly Ala  
85 90 95

His Asp Pro Glu Asp Pro His Pro Leu Ser Val Val Ala Gly Arg Pro  
 100 105 110

Phe Ser Cys Pro Asn His Glu Gly Lys Thr Met Glu Phe Tyr Cys Glu  
 115 120 125

Ala Cys Glu Thr Ala Met Cys Gly Glu Cys Arg Ala Gly Glu His Arg  
 130 135 140

Glu His Gly Thr Val Leu Leu Arg Asp Val Val Glu Gln His Lys Ala  
 145 150 155 160

Ala Leu Gln Arg Gln Leu Glu Ala Val Arg Gly Arg Leu Pro Gln Leu  
 165 170 175

Ser Ala Ala Ile Ala Leu Val Gly Gly Ile Ser Gln Gln Leu Gln Glu  
 180 185 190

Arg Lys Ala Glu Ala Leu Ala Gln Ile Ser Ala Ala Phe Glu Asp Leu  
 195 200 205

Glu Gln Ala Leu Gln Gln Arg Lys Gln Ala Leu Val Ser Asp Leu Glu  
 210 215 220

Thr Ile Cys Gly Ala Lys Gln Lys Val Leu Gln Thr Gln Leu Asp Thr  
 225 230 235 240

Leu Arg Gln Gly Gln Glu His Ile Gly Ser Ser Cys Ser Phe Ala Glu  
 245 250 255

Gln Ala Leu Arg Leu Gly Ser Ala Pro Glu Val Leu Leu Val Arg Lys  
 260 265 270

His Met Arg Glu Arg Leu Ala Ala Leu Ala Ala Gln Ala Phe Pro Glu  
 275 280 285

Arg Pro His Glu Asn Ala Gln Leu Glu Leu Val Leu Glu Val Asp Gly  
 290 295 300

Leu Arg Arg Ser Val Leu Asn Leu Gly Ala Leu Leu Thr Thr Ser Ala  
 305 310 315 320

Thr Ala His Glu Thr Val Ala Thr Gly Glu Gly Leu Arg Gln Ala Leu  
 325 330 335

Val Gly Gln Pro Ala Ser Leu Thr Val Thr Ala Lys Asp Lys Asp Gly

340	345	350
Arg Leu Val Arg Thr Gly Ser Ala Glu Leu Arg Ala Glu Ile Thr Gly		
355	360	365
Pro Asp Gly Thr Arg Leu Pro Val Pro Val Val Asp His Lys Asn Gly		
370	375	380
Thr Tyr Glu Leu Val Tyr Thr Ala Arg Thr Glu Gly Glu Leu Leu Leu		
385	390	395
		400
Ser Val Leu Leu Tyr Gly Gln Pro Val Arg Gly Ser Pro Phe Arg Val		
	405	410
		415
Arg Ala Leu Arg Pro Gly Asp Leu Pro Pro Ser Pro Asp Asp Val Lys		
	420	425
		430
Arg Arg Val Lys Ser Pro Gly Gly Pro Gly Ser His Val Arg Gln Lys		
	435	440
		445
Ala Val Arg Arg Pro Ser Ser Met Tyr Ser Thr Gly Gly Lys Arg Lys		
	450	455
		460
Asp Asn Pro Ile Glu Asp Glu Leu Val Phe Arg Val Gly Ser Arg Gly		
	465	470
		475
		480
Arg Glu Lys Gly Glu Phe Thr Asn Leu Gln Gly Val Ser Ala Ala Ser		
	485	490
		495
Ser Gly Arg Ile Val Val Ala Asp Ser Asn Asn Gln Cys Ile Gln Val		
	500	505
		510
Phe Ser Asn Glu Gly Gln Phe Lys Phe Arg Phe Gly Val Arg Gly Arg		
	515	520
		525
Ser Pro Gly Gln Leu Gln Arg Pro Thr Gly Val Ala Val Asp Thr Asn		
	530	535
		540
Gly Asp Ile Ile Val Ala Asp Tyr Asp Asn Arg Trp Val Ser Ile Phe		
	545	550
		555
		560
Ser Pro Glu Gly Lys Phe Lys Thr Lys Ile Gly Ala Gly Arg Leu Met		
	565	570
		575
Gly Pro Lys Gly Val Ala Val Asp Arg Asn Gly His Ile Ile Val Val		
	580	585
		590

Asp Asn Lys Ser Cys Cys Val Phe Thr Phe Gln Pro Asn Gly Lys Leu  
 595 600 605

Val Gly Arg Phe Gly Gly Arg Gly Ala Thr Asp Arg His Phe Ala Gly  
 610 615 620

Pro His Phe Val Ala Val Ser Asn Lys Asn Glu Val Val Val Thr Asp  
 625 630 635 640

Phe His Asn His Ser Glu Lys Val Tyr Ser Ala Asp Gly Glu Phe Leu  
 645 650 655

Phe Lys Phe Gly Ser His Gly Glu Gly Asn Gly Gln Phe Asn Ala Pro  
 660 665 670

Thr Gly Val Ala Val Asp Ser Asn Gly Asn Ile Ile Val Ala Asp Trp  
 675 680 685

Gly Asn Ser Arg Ile Gln Val Phe Asp Ser Ser Gly Ser Phe Leu Ser  
 690 695 700

Tyr Ile Asn Thr Ser Ala Glu Pro Leu Tyr Gly Pro Gln Gly Leu Ala  
 705 710 715 720

Leu Thr Ser Asp Gly His Val Val Val Ala Asp Ala Gly Asn His Cys  
 725 730 735

Phe Lys Ala Tyr Arg Tyr Leu Gln  
 740

<210> 87  
 <211> 618  
 <212> PRT  
 <213> Homo sapiens

<400> 87

Met Thr Gln Glu Tyr Asp Asn Lys Arg Pro Val Leu Ala Leu Gln Asn  
 1 5 10 15

Glu Ala Leu Tyr Pro Gln Arg Arg Ser Tyr Thr Ser Glu Asp Glu Ala  
 20 25 30

Trp Lys Ser Phe Leu Glu Asn Pro Leu Thr Ala Ala Thr Lys Ala Met  
 35 40 45

Met Ser Ile Asn Gly Asp Glu Asp Ser Ala Ala Ala Leu Gly Leu Leu  
 50 55 60



Tyr Asp Tyr Tyr Lys Val Pro Arg Glu Arg Arg Ser Ser Thr Ala Lys  
 65 70 75 80

Pro Glu Val Glu His Pro Glu Pro Asp His Ser Lys Arg Asn Ser Ile  
 85 90 95

Pro Ile Val Thr Glu Gln Pro Leu Ile Ser Ala Gly Glu Asn Arg Val  
 100 105 110

Gln Val Leu Lys Asn Val Pro Phe Asn Ile Val Leu Pro His Gly Asn  
 115 120 125

Gln Leu Gly Ile Asp Lys Arg Gly His Leu Thr Ala Pro Asp Thr Thr  
 130 135 140

Val Thr Val Ser Ile Ala Thr Met Pro Thr His Ser Ile Lys Thr Glu  
 145 150 155 160

Thr Gln Pro His Gly Phe Ala Val Gly Ile Pro Pro Ala Val Tyr His  
 165 170 175

Pro Glu Pro Thr Glu Arg Val Val Val Phe Asp Arg Asn Leu Asn Thr  
 180 185 190

Asp Gln Phe Ser Ser Gly Ala Gln Ala Pro Asn Ala Gln Arg Arg Thr  
 195 200 205

Pro Asp Ser Thr Phe Ser Glu Thr Phe Lys Glu Gly Val Gln Glu Val  
 210 215 220

Phe Phe Pro Ser Asp Leu Ser Leu Arg Met Pro Gly Met Asn Ser Glu  
 225 230 235 240

Asp Tyr Val Phe Asp Ser Val Ser Gly Asn Asn Phe Glu Tyr Thr Leu  
 245 250 255

Glu Ala Ser Lys Ser Leu Arg Gln Lys Pro Gly Asp Ser Thr Met Thr  
 260 265 270

Tyr Leu Asn Lys Gly Gln Phe Tyr Pro Ile Thr Leu Lys Glu Val Ser  
 275 280 285

Ser Ser Glu Gly Ile His His Pro Ile Ser Lys Val Arg Ser Val Ile  
 290 295 300

Met Val Val Phe Ala Glu Asp Lys Ser Arg Glu Asp Gln Leu Arg His  
 305 310 315 320  
 Trp Lys Tyr Trp His Ser Arg Gln His Thr Ala Lys Gln Arg Cys Ile  
 325 330 335  
 Asp Ile Ala Asp Tyr Lys Glu Ser Phe Asn Thr Ile Ser Asn Ile Glu  
 340 345 350  
 Glu Ile Ala Tyr Asn Ala Ile Ser Phe Thr Trp Asp Ile Asn Asp Glu  
 355 360 365  
 Ala Lys Val Phe Ile Ser Val Asn Cys Leu Ser Thr Asp Phe Ser Ser  
 370 375 380  
 Gln Lys Gly Val Lys Gly Leu Pro Leu Asn Ile Gln Val Asp Thr Tyr  
 385 390 395 400  
 Ser Tyr Asn Asn Arg Ser Asn Lys Pro Val His Arg Ala Tyr Cys Gln  
 405 410 415  
 Ile Lys Val Phe Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu  
 420 425 430  
 Glu Arg Lys Gln Ser Lys Arg Lys Val Ser Asp Val Lys Val Pro Leu  
 435 440 445  
 Leu Pro Ser His Lys Arg Met Asp Ile Thr Val Phe Lys Pro Phe Ile  
 450 455 460  
 Asp Leu Asp Thr Gln Pro Val Leu Phe Ile Pro Asp Val His Phe Ala  
 465 470 475 480  
 Asn Leu Gln Arg Gly Thr His Val Leu Pro Ile Ala Ser Glu Glu Leu  
 485 490 495  
 Glu Gly Glu Gly Ser Val Leu Lys Arg Gly Pro Tyr Gly Thr Glu Asp  
 500 505 510  
 Asp Phe Ala Val Pro Pro Ser Thr Lys Leu Ala Arg Ile Glu Glu Pro  
 515 520 525  
 Lys Arg Val Leu Leu Tyr Val Arg Lys Glu Ser Glu Glu Val Phe Asp  
 530 535 540  
 Ala Leu Met Leu Lys Thr Pro Ser Leu Lys Gly Leu Met Glu Ala Ile  
 545 550 555 560

Ser Asp Lys Tyr Asp Val Pro His Asp Lys Ile Gly Lys Ile Phe Lys  
565 570 575

Lys Cys Lys Lys Gly Ile Leu Val Asn Met Asp Asp Asn Ile Val Lys  
580 585 590

His Tyr Ser Asn Glu Asp Thr Phe Gln Leu Gln Ile Glu Glu Ala Gly  
595 600 605

Gly Ser Tyr Lys Leu Thr Leu Thr Glu Ile  
610 615

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<210> 88
<211> 531
<212> PRT
<213> Homo sapiens
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<400> 88

Met Asp Gly Ile Val Thr Glu Val Ala Val Gly Val Lys Arg Gly Ser  
1 5 10 15

Asp Glu Leu Leu Ser Gly Ser Val Leu Ser Ser Pro Asn Ser Asn Met  
20 25 30

Ser Ser Met Val Val Thr Ala Asn Gly Asn Asp Ser Lys Lys Phe Lys  
35 40 45

Gly Glu Asp Lys Met Asp Gly Ala Pro Ser Arg Val Leu His Ile Arg  
50 55 60

Lys Leu Pro Gly Glu Val Thr Glu Thr Glu Val Ile Ala Leu Gly Leu  
65 70 75 80

Pro Phe Gly Lys Val Thr Asn Ile Leu Met Leu Lys Gly Lys Asn Gln  
85 90 95

Ala Phe Leu Glu Leu Ala Thr Glu Glu Ala Ala Ile Thr Met Val Asn  
100 105 110

Tyr Tyr Ser Ala Val Thr Pro His Leu Arg Asn Gln Pro Ile Tyr Ile  
115 120 125

Gln Tyr Ser Asn His Lys Glu Leu Lys Thr Asp Asn Thr Leu Asn Gln  
130 135 140

Arg Ala Gln Ala Val Leu Gln Ala Val Thr Ala Val Gln Thr Ala Asn

145		150		155		160
Thr Pro Leu Ser Gly Thr Thr Val Ser Glu Ser Ala Val Thr Pro Ala						
	165			170		175
Gln Ser Pro Val Leu Arg Ile Ile Ile Asp Asn Met Tyr Tyr Pro Val						
	180			185		190
Thr Leu Asp Val Leu His Gln Ile Phe Ser Lys Phe Gly Ala Val Leu						
	195		200		205	
Lys Ile Ile Thr Phe Thr Lys Asn Asn Gln Phe Gln Ala Leu Leu Gln						
	210		215		220	
Tyr Gly Asp Pro Val Asn Ala Gln Gln Ala Lys Leu Ala Leu Asp Gly						
	225		230		235	240
Gln Asn Ile Tyr Asn Ala Cys Cys Thr Leu Arg Ile Asp Phe Ser Lys						
		245		250		255
Leu Val Asn Leu Asn Val Lys Tyr Asn Asn Asp Lys Ser Arg Asp Tyr						
	260		265			270
Thr Arg Pro Asp Leu Pro Ser Gly Asp Gly Gln Pro Ala Leu Asp Pro						
	275		280			285
Ala Ile Ala Ala Ala Phe Ala Lys Glu Thr Ser Leu Leu Ala Val Pro						
	290		295			300
Gly Ala Leu Ser Pro Leu Ala Ile Pro Asn Ala Ala Ala Ala Ala Ala						
	305		310		315	320
Ala Ala Ala Ala Gly Arg Val Gly Met Pro Gly Val Ser Ala Gly Gly						
		325		330		335
Asn Thr Val Leu Leu Val Ser Asn Leu Asn Glu Glu Met Val Thr Pro						
	340		345			350
Gln Ser Leu Phe Thr Leu Phe Gly Val Tyr Gly Asp Val Gln Arg Val						
	355		360			365
Lys Ile Leu Tyr Asn Lys Lys Asp Ser Ala Leu Ile Gln Met Ala Asp						
	370		375			380
Gly Asn Gln Ser Gln Leu Ala Met Asn His Leu Asn Gly Gln Lys Met						
	385		390		395	400

Tyr Gly Lys Ile Ile Arg Val Thr Leu Ser Lys His Gln Thr Val Gln  
 405 410 415

Leu Pro Arg Glu Gly Leu Asp Asp Gln Gly Leu Thr Lys Asp Phe Gly  
 420 425 430

Asn Ser Pro Leu His Arg Phe Lys Lys Pro Gly Ser Lys Asn Phe Gln  
 435 440 445

Asn Ile Phe Pro Pro Ser Ala Thr Leu His Leu Ser Asn Ile Pro Pro  
 450 455 460

Ser Val Ala Glu Glu Asp Leu Arg Thr Leu Phe Ala Asn Thr Gly Gly  
 465 470 475 480

Thr Val Lys Ala Phe Lys Phe Phe Gln Asp His Lys Met Ala Leu Leu  
 485 490 495

Gln Met Ala Thr Val Glu Glu Ala Ile Gln Ala Leu Ile Asp Leu His  
 500 505 510

Asn Tyr Asn Leu Gly Glu Asn His His Leu Arg Val Ser Phe Ser Lys  
 515 520 525

Ser Thr Ile  
 530

<210> 89  
 <211> 521  
 <212> PRT  
 <213> Homo sapiens

<400> 89

Met Asn Ser Ser Thr Pro Ser Thr Ala Asn Gly Asn Asp Ser Lys Lys  
 1 5 10 15

Phe Lys Arg Asp Arg Pro Pro Cys Ser Pro Ser Arg Val Leu His Leu  
 20 25 30

Arg Lys Ile Pro Cys Asp Val Thr Glu Ala Glu Ile Ile Ser Leu Gly  
 35 40 45

Leu Pro Phe Gly Lys Val Thr Asn Leu Leu Met Leu Lys Gly Lys Ser  
 50 55 60

Gln Ala Phe Leu Glu Met Ala Ser Glu Glu Ala Ala Val Thr Met Val  
 65 70 75 80

Asn Tyr Tyr Thr Pro Ile Thr Pro His Leu Arg Ser Gln Pro Val Tyr  
                                     85                                    90                                    95

Ile Gln Tyr Ser Asn His Arg Glu Leu Lys Thr Asp Asn Leu Pro Asn  
                                     100                                    105                                    110

Gln Ala Arg Ala Gln Ala Ala Leu Gln Ala Val Ser Ala Val Gln Ser  
                                     115                                    120                                    125

Gly Ser Leu Ala Leu Ser Gly Gly Pro Ser Asn Glu Gly Thr Val Leu  
                                     130                                    135                                    140

Pro Gly Gln Ser Pro Val Leu Arg Ile Ile Ile Glu Asn Leu Phe Tyr  
                                     145                                    150                                    155                                    160

Pro Val Thr Leu Glu Val Leu His Gln Ile Phe Ser Lys Phe Gly Thr  
                                     165                                    170                                    175

Val Leu Lys Ile Ile Thr Phe Thr Lys Asn Asn Gln Phe Gln Ala Leu  
                                     180                                    185                                    190

Leu Gln Tyr Ala Asp Pro Val Asn Ala His Tyr Ala Lys Met Ala Leu  
                                     195                                    200                                    205

Asp Gly Gln Asn Ile Tyr Asn Ala Cys Cys Thr Leu Arg Ile Asp Phe  
                                     210                                    215                                    220

Ser Lys Leu Thr Ser Leu Asn Val Lys Tyr Asn Asn Asp Lys Ser Arg  
                                     225                                    230                                    235                                    240

Asp Phe Thr Arg Leu Asp Leu Pro Thr Gly Asp Gly Gln Pro Ser Leu  
                                     245                                    250                                    255

Glu Pro Pro Met Ala Ala Ala Phe Gly Ala Pro Gly Ile Ile Ser Ser  
                                     260                                    265                                    270

Pro Tyr Ala Gly Ala Ala Gly Phe Ala Pro Ala Ile Gly Phe Pro Gln  
                                     275                                    280                                    285

Ala Thr Gly Leu Ser Val Pro Ala Val Pro Gly Ala Leu Gly Pro Leu  
                                     290                                    295                                    300

Thr Ile Thr Ser Ser Ala Val Thr Gly Arg Met Ala Ile Pro Gly Ala  
                                     305                                    310                                    315                                    320

Ser Gly Ile Pro Gly Asn Ser Val Leu Leu Val Thr Asn Leu Asn Pro  
 325 330 335

Asp Leu Ile Thr Pro His Gly Leu Phe Ile Leu Phe Gly Val Tyr Gly  
 340 345 350

Asp Val His Arg Val Lys Ile Met Phe Asn Lys Lys Glu Asn Ala Leu  
 355 360 365

Val Gln Met Ala Asp Ala Asn Gln Ala Gln Leu Ala Met Asn His Leu  
 370 375 380

Ser Gly Gln Arg Leu Tyr Gly Lys Val Leu Arg Ala Thr Leu Ser Lys  
 385 390 395 400

His Gln Ala Val Gln Leu Pro Arg Glu Gly Gln Glu Asp Gln Gly Leu  
 405 410 415

Thr Lys Asp Phe Ser Asn Ser Pro Leu His Arg Phe Lys Lys Pro Gly  
 420 425 430

Ser Lys Asn Phe Gln Asn Ile Phe Pro Pro Ser Ala Thr Leu His Leu  
 435 440 445

Ser Asn Ile Pro Pro Ser Val Thr Val Asp Asp Leu Lys Asn Leu Phe  
 450 455 460

Ile Glu Ala Gly Cys Ser Val Lys Ala Phe Lys Phe Phe Gln Lys Asp  
 465 470 475 480

Arg Lys Met Ala Leu Ile Gln Leu Gly Ser Val Glu Glu Ala Ile Gln  
 485 490 495

Ala Leu Ile Glu Leu His Asn His Asp Leu Gly Glu Asn His His Leu  
 500 505 510

Arg Val Ser Phe Ser Lys Ser Thr Ile  
 515 520

<210> 90

<211> 557

<212> PRT

<213> Homo sapiens

<400> 90

Met Asp Gly Ile Val Pro Asp Ile Ala Val Gly Thr Lys Arg Gly Ser  
 1 5 10 15

Asp Glu Leu Phe Ser Thr Cys Val Thr Asn Gly Pro Phe Ile Met Ser  
 20 25 30  
 Ser Asn Ser Ala Ser Ala Ala Asn Gly Asn Asp Ser Lys Lys Phe Lys  
 35 40 45  
 Gly Asp Ser Arg Ser Ala Gly Val Pro Ser Arg Val Ile His Ile Arg  
 50 55 60  
 Lys Leu Pro Ile Asp Val Thr Glu Gly Glu Val Ile Ser Leu Gly Leu  
 65 70 75 80  
 Pro Phe Gly Lys Val Thr Asn Leu Leu Met Leu Lys Gly Lys Asn Gln  
 85 90 95  
 Ala Phe Ile Glu Met Asn Thr Glu Glu Ala Ala Asn Thr Met Val Asn  
 100 105 110  
 Tyr Tyr Thr Ser Val Thr Pro Val Leu Arg Gly Gln Pro Ile Tyr Ile  
 115 120 125  
 Gln Phe Ser Asn His Lys Glu Leu Lys Thr Asp Ser Ser Pro Asn Gln  
 130 135 140  
 Ala Arg Ala Gln Ala Ala Leu Gln Ala Val Asn Ser Val Gln Ser Gly  
 145 150 155 160  
 Asn Leu Ala Leu Ala Ala Ser Ala Ala Ala Val Asp Ala Gly Met Ala  
 165 170 175  
 Met Ala Gly Gln Ser Pro Val Leu Arg Ile Ile Val Glu Asn Leu Phe  
 180 185 190  
 Tyr Pro Val Thr Leu Asp Val Leu His Gln Ile Phe Ser Lys Phe Gly  
 195 200 205  
 Thr Val Leu Lys Ile Ile Thr Phe Thr Lys Asn Asn Gln Phe Gln Ala  
 210 215 220  
 Leu Leu Gln Tyr Ala Asp Pro Val Ser Ala Gln His Ala Lys Leu Ser  
 225 230 235 240  
 Leu Asp Gly Gln Asn Ile Tyr Asn Ala Cys Cys Thr Leu Arg Ile Asp  
 245 250 255  
 Phe Ser Lys Leu Thr Ser Leu Asn Val Lys Tyr Asn Asn Asp Lys Ser



260	265	270
Arg Asp Tyr Thr Arg Pro Asp Leu Pro Ser Gly Asp Ser Gln Pro Ser		
275	280	285
Leu Asp Gln Thr Met Ala Ala Ala Phe Gly Ala Pro Gly Ile Ile Ser		
290	295	300
Ala Ser Pro Tyr Ala Gly Ala Gly Phe Pro Pro Thr Phe Ala Ile Pro		
305	310	315
Gln Ala Ala Gly Leu Ser Val Pro Asn Val His Gly Ala Leu Ala Pro		
	325	330
		335
Leu Ala Ile Pro Ser Ala Ala Ala Ala Ala Ala Ala Ala Gly Arg Ile		
	340	345
		350
Ala Ile Pro Gly Leu Ala Gly Ala Gly Asn Ser Val Leu Leu Val Ser		
	355	360
		365
Asn Leu Asn Pro Glu Arg Val Thr Pro Gln Ser Leu Phe Ile Leu Phe		
	370	375
		380
Gly Val Tyr Gly Asp Val Gln Arg Val Lys Ile Leu Phe Asn Lys Lys		
385	390	395
		400
Glu Asn Ala Leu Val Gln Met Ala Asp Gly Asn Gln Ala Gln Leu Ala		
	405	410
		415
Met Ser His Leu Asn Gly His Lys Leu His Gly Lys Pro Ile Arg Ile		
	420	425
		430
Thr Leu Ser Lys His Gln Asn Val Gln Leu Pro Arg Glu Gly Gln Glu		
	435	440
		445
Asp Gln Gly Leu Thr Lys Asp Tyr Gly Asn Ser Pro Leu His Arg Phe		
	450	455
		460
Lys Lys Pro Gly Ser Lys Asn Phe Gln Asn Ile Phe Pro Pro Ser Ala		
465	470	475
		480
Thr Leu His Leu Ser Asn Ile Pro Pro Ser Val Ser Glu Glu Asp Leu		
	485	490
		495
Lys Val Leu Phe Ser Ser Asn Gly Gly Val Val Lys Gly Phe Lys Phe		
	500	505
		510

Phe Gln Lys Asp Arg Lys Met Ala Leu Ile Gln Met Gly Ser Val Glu  
 515 520 525

Glu Ala Val Gln Ala Leu Ile Asp Leu His Asn His Asp Leu Gly Glu  
 530 535 540

Asn His His Leu Arg Val Ser Phe Ser Lys Ser Thr Ile  
 545 550 555

<210> 91  
 <211> 534  
 <212> PRT  
 <213> Homo sapiens

<400> 91

Met Ile Trp Tyr Ile Leu Ile Ile Gly Ile Leu Leu Pro Gln Ser Leu  
 1 5 10 15

Ala His Pro Gly Phe Phe Thr Ser Ile Gly Gln Met Thr Asp Leu Ile  
 20 25 30

His Thr Glu Lys Asp Leu Val Thr Ser Leu Lys Asp Tyr Ile Lys Ala  
 35 40 45

Glu Glu Asp Lys Leu Glu Gln Ile Lys Lys Trp Ala Glu Lys Leu Asp  
 50 55 60

Arg Leu Thr Ser Thr Ala Thr Lys Asp Pro Glu Gly Phe Val Gly His  
 65 70 75 80

Pro Val Asn Ala Phe Lys Leu Met Lys Arg Leu Asn Thr Glu Trp Ser  
 85 90 95

Glu Leu Glu Asn Leu Val Leu Lys Asp Met Ser Asp Gly Phe Ile Ser  
 100 105 110

Asn Leu Thr Ile Gln Arg Pro Val Leu Ser Asn Asp Glu Asp Gln Val  
 115 120 125

Gly Ala Ala Lys Ala Leu Leu Arg Leu Gln Asp Thr Tyr Asn Leu Asp  
 130 135 140

Thr Asp Thr Ile Ser Lys Gly Asn Leu Pro Gly Val Lys His Lys Ser  
 145 150 155 160

Phe Leu Thr Ala Glu Asp Cys Phe Glu Leu Gly Lys Val Ala Tyr Thr  
 165 170 175

Glu Ala Asp Tyr Tyr His Thr Glu Leu Trp Met Glu Gln Ala Leu Arg  
 180 185 190

Gln Leu Asp Glu Gly Glu Ile Ser Thr Ile Asp Lys Val Ser Val Leu  
 195 200 205

Asp Tyr Leu Ser Tyr Ala Val Tyr Gln Gln Gly Asp Leu Asp Lys Ala  
 210 215 220

Leu Leu Leu Thr Lys Lys Leu Leu Glu Leu Asp Pro Glu His Gln Arg  
 225 230 235 240

Ala Asn Gly Asn Leu Lys Tyr Phe Glu Tyr Ile Met Ala Lys Glu Lys  
 245 250 255

Asp Val Asn Lys Ser Ala Ser Asp Asp Gln Ser Asp Gln Lys Thr Thr  
 260 265 270

Pro Lys Lys Lys Gly Val Ala Val Asp Tyr Leu Pro Glu Arg Gln Lys  
 275 280 285

Tyr Glu Met Leu Cys Arg Gly Glu Gly Ile Lys Met Thr Pro Arg Arg  
 290 295 300

Gln Lys Lys Leu Phe Cys Arg Tyr His Asp Gly Asn Arg Asn Pro Lys  
 305 310 315 320

Phe Ile Leu Ala Pro Ala Lys Gln Glu Asp Glu Trp Asp Lys Pro Arg  
 325 330 335

Ile Ile Arg Phe His Asp Ile Ile Ser Asp Ala Glu Ile Glu Ile Val  
 340 345 350

Lys Asp Leu Ala Lys Pro Arg Leu Ser Arg Ala Thr Val His Asp Pro  
 355 360 365

Glu Thr Gly Lys Leu Thr Thr Ala Gln Tyr Arg Val Ser Lys Ser Ala  
 370 375 380

Trp Leu Ser Gly Tyr Glu Asn Pro Val Val Ser Arg Ile Asn Met Arg  
 385 390 395 400

Ile Gln Asp Leu Thr Gly Leu Asp Val Ser Thr Ala Glu Glu Leu Gln  
 405 410 415

Val Ala Asn Tyr Gly Val Gly Gly Gln Tyr Glu Pro His Phe Asp Phe  
 420 425 430

Ala Arg Lys Asp Glu Pro Asp Ala Phe Lys Glu Leu Gly Thr Gly Asn  
 435 440 445

Arg Ile Ala Thr Trp Leu Phe Tyr Met Ser Asp Val Ser Ala Gly Gly  
 450 455 460

Ala Thr Val Phe Pro Glu Val Gly Ala Ser Val Trp Pro Lys Lys Gly  
 465 470 475 480

Thr Ala Val Phe Trp Tyr Asn Leu Phe Ala Ser Gly Glu Gly Asp Tyr  
 485 490 495

Ser Thr Arg His Ala Ala Cys Pro Val Leu Val Gly Asn Lys Trp Val  
 500 505 510

Ser Asn Lys Trp Leu His Glu Arg Gly Gln Glu Phe Arg Arg Pro Cys  
 515 520 525

Thr Leu Ser Glu Leu Glu  
 530

<210> 92  
 <211> 535  
 <212> PRT  
 <213> Homo sapiens

<400> 92

Met Lys Leu Trp Val Ser Ala Leu Leu Met Ala Trp Phe Gly Val Leu  
 1 5 10 15

Ser Cys Val Gln Ala Glu Phe Phe Thr Ser Ile Gly His Met Thr Asp  
 20 25 30

Leu Ile Tyr Ala Glu Lys Glu Leu Val Gln Ser Leu Lys Glu Tyr Ile  
 35 40 45

Leu Val Glu Glu Ala Lys Leu Ser Lys Ile Lys Ser Trp Ala Asn Lys  
 50 55 60

Met Glu Ala Leu Thr Ser Lys Ser Ala Ala Asp Ala Glu Gly Tyr Leu  
 65 70 75 80

Ala His Pro Val Asn Ala Tyr Lys Leu Val Lys Arg Leu Asn Thr Asp  
 85 90 95

Trp Pro Ala Leu Glu Asp Leu Val Leu Gln Asp Ser Ala Ala Gly Phe  
 100 105 110  
 Ile Ala Asn Leu Ser Val Gln Arg Gln Phe Phe Pro Thr Asp Glu Asp  
 115 120 125  
 Glu Ile Gly Ala Ala Lys Ala Leu Met Arg Leu Gln Asp Thr Tyr Arg  
 130 135 140  
 Leu Asp Pro Gly Thr Ile Ser Arg Gly Glu Leu Pro Gly Thr Lys Tyr  
 145 150 155 160  
 Gln Ala Met Leu Ser Val Asp Asp Cys Phe Gly Met Gly Arg Ser Ala  
 165 170 175  
 Tyr Asn Glu Gly Asp Tyr Tyr His Thr Val Leu Trp Met Glu Gln Val  
 180 185 190  
 Leu Lys Gln Leu Asp Ala Gly Glu Glu Ala Thr Thr Thr Lys Ser Gln  
 195 200 205  
 Val Leu Asp Tyr Leu Ser Tyr Ala Val Phe Gln Leu Gly Asp Leu His  
 210 215 220  
 Arg Ala Leu Glu Leu Thr Arg Arg Leu Leu Ser Leu Asp Pro Ser His  
 225 230 235 240  
 Glu Arg Ala Gly Gly Asn Leu Arg Tyr Phe Glu Gln Leu Leu Glu Glu  
 245 250 255  
 Glu Arg Glu Lys Thr Leu Thr Asn Gln Thr Glu Ala Glu Leu Ala Thr  
 260 265 270  
 Pro Glu Gly Ile Tyr Glu Arg Pro Val Asp Tyr Leu Pro Glu Arg Asp  
 275 280 285  
 Val Tyr Glu Ser Leu Cys Arg Gly Glu Gly Val Lys Leu Thr Pro Arg  
 290 295 300  
 Arg Gln Lys Arg Leu Phe Cys Arg Tyr His His Gly Asn Arg Ala Pro  
 305 310 315 320  
 Gln Leu Leu Ile Ala Pro Phe Lys Glu Glu Asp Glu Trp Asp Ser Pro  
 325 330 335  
 His Ile Val Arg Tyr Tyr Asp Val Met Ser Asp Glu Glu Ile Glu Arg

340 345 350  
 Ile Lys Glu Ile Ala Lys Pro Lys Leu Ala Arg Ala Thr Val Arg Asp  
 355 360 365  
 Pro Lys Thr Gly Val Leu Thr Val Ala Ser Tyr Arg Val Ser Lys Ser  
 370 375 380  
 Ser Trp Leu Glu Glu Asp Asp Asp Pro Val Val Ala Arg Val Asn Arg  
 385 390 395 400  
 Arg Met Gln His Ile Thr Gly Leu Thr Val Lys Thr Ala Glu Leu Leu  
 405 410 415  
 Gln Val Ala Asn Tyr Gly Val Gly Gly Gln Tyr Glu Pro His Phe Asp  
 420 425 430  
 Phe Ser Arg Asn Asp Glu Arg Asp Thr Phe Lys His Leu Gly Thr Gly  
 435 440 445  
 Asn Arg Val Ala Thr Phe Leu Asn Tyr Met Ser Asp Val Glu Ala Gly  
 450 455 460  
 Gly Ala Thr Val Phe Pro Asp Leu Gly Ala Ala Ile Trp Pro Lys Lys  
 465 470 475 480  
 Gly Thr Ala Val Phe Trp Tyr Asn Leu Leu Arg Ser Gly Glu Gly Asp  
 485 490 495  
 Tyr Arg Thr Arg His Ala Ala Cys Pro Val Leu Val Gly Cys Lys Trp  
 500 505 510  
 Val Ser Asn Lys Trp Phe His Glu Arg Gly Gln Glu Phe Leu Arg Pro  
 515 520 525  
 Cys Gly Ser Thr Glu Val Asp  
 530 535  
 <210> 93  
 <211> 755  
 <212> PRT  
 <213> Homo sapiens  
 <400> 93  
 Met Glu Ala Val Ile Glu Lys Glu Cys Ser Ala Leu Gly Gly Leu Phe  
 1 5 10 15

Gln Thr Ile Ile Ser Asp Met Lys Gly Ser Tyr Pro Val Trp Glu Asp  
 20 25 30  
 Phe Ile Asn Lys Ala Gly Lys Leu Gln Ser Gln Leu Arg Thr Thr Val  
 35 40 45  
 Val Ala Ala Ala Ala Phe Leu Asp Ala Phe Gln Lys Val Ala Asp Met  
 50 55 60  
 Ala Thr Asn Thr Arg Gly Gly Thr Arg Glu Ile Gly Ser Ala Leu Thr  
 65 70 75 80  
 Arg Met Cys Met Arg His Arg Ser Ile Glu Ala Lys Leu Arg Gln Phe  
 85 90 95  
 Ser Ser Ala Leu Ile Asp Cys Leu Ile Asn Pro Leu Gln Glu Gln Met  
 100 105 110  
 Glu Glu Trp Lys Lys Val Ala Asn Gln Leu Asp Lys Asp His Ala Lys  
 115 120 125  
 Glu Tyr Lys Lys Ala Arg Gln Glu Ile Lys Lys Lys Ser Ser Asp Thr  
 130 135 140  
 Leu Lys Leu Gln Lys Lys Ala Lys Lys Gly Arg Gly Asp Ile Gln Pro  
 145 150 155 160  
 Gln Leu Asp Ser Ala Leu Gln Asp Val Asn Asp Lys Tyr Leu Leu Leu  
 165 170 175  
 Glu Glu Thr Glu Lys Gln Ala Val Arg Lys Ala Leu Ile Glu Glu Arg  
 180 185 190  
 Gly Arg Phe Cys Thr Phe Ile Ser Met Leu Arg Pro Val Ile Glu Glu  
 195 200 205  
 Glu Ile Ser Met Leu Gly Glu Ile Thr His Leu Gln Thr Ile Ser Glu  
 210 215 220  
 Asp Leu Lys Ser Leu Thr Met Asp Pro His Lys Leu Pro Ser Ser Ser  
 225 230 235 240  
 Glu Gln Val Ile Leu Asp Leu Lys Gly Ser Asp Tyr Ser Trp Ser Tyr  
 245 250 255  
 Gln Thr Pro Pro Ser Ser Pro Ser Thr Thr Met Ser Arg Lys Ser Ser  
 260 265 270

Val Cys Ser Ser Leu Asn Ser Val Asn Ser Ser Asp Ser Arg Ser Ser  
 275 280 285

Gly Ser His Ser His Ser Pro Ser Ser His Tyr Arg Tyr Arg Ser Ser  
 290 295 300

Asn Leu Ala Gln Gln Ala Pro Val Arg Leu Ser Ser Val Ser Ser His  
 305 310 315 320

Asp Ser Gly Phe Ile Ser Gln Asp Ala Phe Gln Ser Lys Ser Pro Ser  
 325 330 335

Pro Met Pro Pro Glu Ala Pro Asn Gln Leu Ser Asn Gly Phe Ser His  
 340 345 350

Tyr Ser Leu Ser Ser Glu Ser His Val Gly Pro Thr Gly Ala Gly Leu  
 355 360 365

Phe Pro His Cys Leu Pro Ala Ser Arg Leu Leu Pro Arg Val Thr Ser  
 370 375 380

Val His Leu Pro Asp Tyr Ala His Tyr Tyr Thr Ile Gly Pro Gly Met  
 385 390 395 400

Phe Pro Ser Ser Gln Ile Pro Ser Trp Lys Asp Trp Ala Lys Pro Gly  
 405 410 415

Pro Tyr Asp Gln Pro Leu Val Asn Thr Leu Gln Arg Arg Lys Glu Lys  
 420 425 430

Arg Glu Pro Asp Pro Asn Gly Gly Gly Pro Thr Thr Ala Ser Gly Pro  
 435 440 445

Pro Ala Ala Ala Glu Glu Ala Gln Arg Pro Arg Ser Met Thr Val Ser  
 450 455 460

Ala Ala Thr Arg Pro Gly Glu Glu Met Glu Ala Cys Glu Glu Leu Ala  
 465 470 475 480

Leu Ala Leu Ser Arg Gly Leu Gln Leu Asp Thr Gln Arg Ser Ser Arg  
 485 490 495

Asp Ser Leu Gln Cys Ser Ser Gly Tyr Ser Thr Gln Thr Thr Thr Pro  
 500 505 510



Cys Cys Ser Glu Asp Thr Ile Pro Ser Gln Val Ser Asp Tyr Asp Tyr  
           515                          520                          525

Phe Ser Val Ser Gly Asp Gln Glu Ala Asp Gln Gln Glu Phe Asp Lys  
           530                          535                          540

Ser Ser Thr Ile Pro Arg Asn Ser Asp Ile Ser Gln Ser Tyr Arg Arg  
   545                          550                          555                          560

Met Phe Gln Ala Lys Arg Pro Ala Ser Thr Ala Gly Leu Pro Thr Thr  
                           565                          570                          575

Leu Gly Pro Ala Met Val Thr Pro Gly Val Ala Thr Ile Arg Arg Thr  
                           580                          585                          590

Pro Ser Thr Lys Pro Ser Val Arg Arg Gly Thr Ile Gly Ala Gly Pro  
           595                          600                          605

Ile Pro Ile Lys Thr Pro Val Ile Pro Val Lys Thr Pro Thr Val Pro  
   610                          615                          620

Asp Leu Pro Gly Val Met Pro Ala Pro Pro Asp Gly Pro Glu Glu Arg  
   625                          630                          635                          640

Gly Glu His Ser Pro Glu Ser Pro Ser Val Gly Glu Gly Pro Gln Gly  
                           645                          650                          655

Val Thr Ser Met Pro Ser Ser Met Trp Ser Gly Gln Ala Ser Val Asn  
                           660                          665                          670

Pro Pro Leu Pro Gly Pro Lys Pro Ser Ile Pro Glu Glu His Arg Gln  
           675                          680                          685

Ala Ile Pro Glu Ser Glu Ala Glu Asp Gln Glu Arg Glu Pro Pro Ser  
   690                          695                          700

Ala Thr Val Ser Pro Gly Gln Ile Pro Glu Ser Asp Pro Ala Asp Leu  
   705                          710                          715                          720

Ser Pro Arg Asp Thr Pro Gln Gly Glu Asp Met Leu Asn Ala Ile Arg  
                           725                          730                          735

Arg Gly Val Lys Leu Lys Lys Thr Thr Thr Asn Asp Arg Ser Ala Pro  
                           740                          745                          750

Arg Phe Ser  
       755

<210> 94  
 <211> 211  
 <212> PRT  
 <213> Homo sapiens

<400> 94

Met Cys Met Arg His Arg Ser Ile Glu Thr Lys Leu Arg Gln Phe Thr  
 1 5 10 15

Asn Ala Leu Leu Glu Ser Leu Ile Asn Pro Leu Gln Glu Arg Ile Glu  
 20 25 30

Asp Trp Lys Lys Ala Ala Asn Gln Leu Asp Lys Asp His Ala Lys Glu  
 35 40 45

Tyr Lys Arg Ala Arg His Glu Ile Lys Lys Lys Ser Ser Asp Thr Leu  
 50 55 60

Lys Leu Gln Lys Lys Ala Arg Lys Gly Lys Gly Asp Leu Gln Pro Gln  
 65 70 75 80

Leu Asp Ser Ala Leu Gln Asp Val Asn Asp Met Tyr Leu Leu Leu Glu  
 85 90 95

Glu Thr Glu Lys Gln Ala Val Arg Arg Ala Leu Ile Glu Glu Arg Gly  
 100 105 110

Arg Phe Cys Thr Phe Ile Thr Phe Leu Gln Pro Val Val Asn Gly Glu  
 115 120 125

Leu Thr Met Leu Gly Glu Ile Thr His Leu Gln Gly Ile Ile Asp Asp  
 130 135 140

Leu Val Val Leu Thr Ala Glu Pro His Lys Leu Pro Pro Ala Ser Glu  
 145 150 155 160

Gln Val Ile Lys Asp Leu Lys Gly Ser Asp Tyr Ser Trp Ser Tyr Gln  
 165 170 175

Thr Pro Pro Ser Val Pro Ser Glu Pro Phe Val Ser Phe Leu Ser Val  
 180 185 190

Arg Phe Trp Lys Asn Ser Pro Leu Leu Pro Ala Pro Ser Thr Pro Ser  
 195 200 205

Ser Pro Ile

210

<210> 95  
 <211> 117  
 <212> PRT  
 <213> Homo sapiens  
 <400> 95

Met Arg Leu Arg Gln Ala Pro Glu Ser Arg Lys Val Phe Ile Gln Arg  
 1 5 10 15

Asp Tyr Ser Ser Gly Thr Gly Cys Gln Phe Gln Thr Met Phe Ser Met  
 20 25 30

Glu Leu Glu Asn Gln Ile Asp Arg Gln Gln Phe Glu Glu Ile Val Gln  
 35 40 45

Thr Leu Asn Asn Leu Tyr Ala Glu Ala Glu Lys Leu Gly Gly Gln Ser  
 50 55 60

Tyr Leu Glu Gly Cys Leu Ala Cys Leu Thr Ala Tyr Thr Ile Phe Leu  
 65 70 75 80

Cys Leu Glu Thr His Tyr Gln Lys Leu Leu Lys Lys Val Ser Lys Cys  
 85 90 95

Ile Gln Glu Gln Asn Glu Lys Ile Tyr Val Pro Gln Gly Leu Leu Leu  
 100 105 110

Thr Asp Ser Ile Glu  
 115

<210> 96  
 <211> 104  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 96

Met Glu Asn Arg Ile Asp Arg Gln Gln Phe Glu Glu Thr Val Arg Thr  
 1 5 10 15

Leu Asn Asn Leu Tyr Ala Glu Ala Glu Lys Leu Gly Gly Gln Ser Tyr  
 20 25 30

Leu Glu Gly Cys Leu Ala Cys Leu Thr Ala Tyr Thr Ile Phe Leu Cys  
 35 40 45

Met Glu Thr His Tyr Glu Lys Val Leu Lys Lys Val Ser Lys Tyr Ile

50                                      55                                      60  
 Gln Glu Gln Asn Glu Lys Ile Tyr Ala Pro Gln Gly Leu Leu Leu Thr  
 65                                      70                                      75                                      80  
 Asp Pro Ile Glu Arg Gly Leu Arg Val Ile Glu Ile Thr Ile Tyr Glu  
                                     85                                      90                                      95  
 Asp Arg Gly Met Ser Ser Gly Arg  
                                     100  
 <210> 97  
 <211> 890  
 <212> PRT  
 <213> Homo sapiens  
 <400> 97  
 Met Asp Ser Asn Thr Ala Pro Leu Gly Pro Ser Cys Pro Gln Pro Pro  
 1                                      5                                      10                                      15  
 Pro Ala Pro Gln Pro Gln Ala Arg Ser Arg Leu Asn Ala Thr Ala Ser  
                                     20                                      25                                      30  
 Leu Glu Gln Glu Arg Ser Glu Arg Pro Arg Ala Pro Gly Pro Gln Ala  
                                     35                                      40                                      45  
 Gly Pro Gly Pro Gly Val Arg Asp Ala Ala Ala Pro Ala Glu Pro Gln  
                                     50                                      55                                      60  
 Ala Gln His Thr Arg Ser Arg Glu Arg Ala Asp Gly Thr Gly Pro Thr  
 65                                      70                                      75                                      80  
 Lys Gly Asp Met Glu Ile Pro Phe Glu Glu Val Leu Glu Arg Ala Lys  
                                     85                                      90                                      95  
 Ala Gly Asp Pro Lys Ala Gln Thr Glu Val Gly Lys His Tyr Leu Gln  
                                     100                                      105                                      110  
 Leu Ala Gly Asp Thr Asp Glu Glu Leu Asn Ser Cys Thr Ala Val Asp  
                                     115                                      120                                      125  
 Trp Leu Val Leu Ala Ala Lys Gln Gly Arg Arg Glu Ala Val Lys Leu  
                                     130                                      135                                      140  
 Leu Arg Arg Cys Leu Ala Asp Arg Arg Gly Ile Thr Ser Glu Asn Glu  
 145                                      150                                      155                                      160

Arg Glu Val Arg Gln Leu Ser Ser Glu Thr Asp Leu Glu Arg Ala Val  
 165 170 175

Arg Lys Ala Ala Leu Val Met Tyr Trp Lys Leu Asn Pro Lys Lys Lys  
 180 185 190

Lys Gln Val Ala Val Ala Glu Leu Leu Glu Asn Val Gly Gln Val Asn  
 195 200 205

Glu His Asp Gly Gly Ala Gln Pro Gly Pro Val Pro Lys Ser Leu Gln  
 210 215 220

Lys Gln Arg Arg Met Leu Glu Arg Leu Val Ser Ser Glu Ser Lys Asn  
 225 230 235 240

Tyr Ile Ala Leu Asp Asp Phe Val Glu Ile Thr Lys Lys Tyr Ala Lys  
 245 250 255

Gly Val Ile Pro Ser Ser Leu Phe Leu Gln Asp Asp Glu Asp Asp Asp  
 260 265 270

Glu Leu Ala Gly Lys Ser Pro Glu Asp Leu Pro Leu Arg Leu Lys Val  
 275 280 285

Val Lys Tyr Pro Leu His Ala Ile Met Glu Ile Lys Glu Tyr Leu Ile  
 290 295 300

Asp Met Ala Ser Arg Ala Gly Met His Trp Leu Ser Thr Ile Ile Pro  
 305 310 315 320

Thr His His Ile Asn Ala Leu Ile Phe Phe Phe Ile Ile Ser Asn Leu  
 325 330 335

Thr Ile Asp Phe Phe Ala Phe Phe Ile Pro Leu Val Ile Phe Tyr Leu  
 340 345 350

Ser Phe Ile Ser Met Val Ile Cys Thr Leu Lys Val Phe Gln Asp Ser  
 355 360 365

Lys Ala Trp Glu Asn Phe Arg Thr Leu Thr Asp Leu Leu Leu Arg Phe  
 370 375 380

Glu Pro Asn Leu Asp Val Glu Gln Ala Glu Val Asn Phe Gly Trp Asn  
 385 390 395 400

His Leu Glu Pro Tyr Ala His Phe Leu Leu Ser Val Phe Phe Val Ile  
 405 410 415

Phe Ser Phe Pro Ile Ala Ser Lys Asp Cys Ile Pro Cys Ser Glu Leu  
 420 425 430

Ala Val Ile Thr Gly Phe Phe Thr Val Thr Ser Tyr Leu Ser Leu Ser  
 435 440 445

Thr His Ala Glu Pro Tyr Thr Arg Arg Ala Leu Ala Thr Glu Val Thr  
 450 455 460

Ala Gly Leu Leu Ser Leu Leu Pro Ser Met Pro Leu Asn Trp Pro Tyr  
 465 470 475 480

Leu Lys Val Leu Gly Gln Thr Phe Ile Thr Val Pro Val Gly His Leu  
 485 490 495

Val Val Leu Asn Val Ser Val Pro Cys Leu Leu Tyr Val Tyr Leu Leu  
 500 505 510

Tyr Leu Phe Phe Arg Met Ala Gln Leu Arg Asn Phe Lys Gly Thr Tyr  
 515 520 525

Cys Tyr Leu Val Pro Tyr Leu Val Cys Phe Met Trp Cys Glu Leu Ser  
 530 535 540

Val Val Ile Leu Leu Glu Ser Thr Gly Leu Gly Leu Leu Arg Ala Ser  
 545 550 555 560

Ile Gly Tyr Phe Leu Phe Leu Phe Ala Leu Pro Ile Leu Val Ala Gly  
 565 570 575

Leu Ala Leu Val Gly Val Leu Gln Phe Ala Arg Trp Phe Thr Ser Leu  
 580 585 590

Glu Leu Thr Lys Ile Ala Val Thr Val Ala Val Cys Ser Val Pro Leu  
 595 600 605

Leu Leu Arg Trp Trp Thr Lys Ala Ser Phe Ser Val Val Gly Met Val  
 610 615 620

Lys Ser Leu Thr Arg Ser Ser Met Val Lys Leu Ile Leu Val Trp Leu  
 625 630 635 640

Thr Ala Ile Val Leu Phe Cys Trp Phe Tyr Val Tyr Arg Ser Glu Gly  
 645 650 655

Met Lys Val Tyr Asn Ser Thr Leu Thr Trp Gln Gln Tyr Gly Ala Leu  
660 665 670

Cys Gly Pro Arg Ala Trp Lys Glu Thr Asn Met Ala Arg Thr Gln Ile  
675 680 685

Leu Cys Ser His Leu Glu Gly His Arg Val Thr Trp Thr Gly Arg Phe  
690 695 700

Lys Tyr Val Arg Val Thr Asp Ile Asp Asn Ser Ala Glu Ser Ala Ile  
705 710 715 720

Asn Met Leu Pro Phe Phe Ile Gly Asp Trp Met Arg Cys Leu Tyr Gly  
725 730 735

Glu Ala Tyr Pro Ala Cys Ser Pro Gly Asn Thr Ser Thr Ala Glu Glu  
740 745 750

Glu Leu Cys Arg Leu Lys Leu Leu Ala Lys His Pro Cys His Ile Lys  
755 760 765

Lys Phe Asp Arg Tyr Lys Phe Glu Ile Thr Val Gly Met Pro Phe Ser  
770 775 780

Ser Gly Ala Asp Gly Ser Arg Ser Arg Glu Glu Asp Asp Val Thr Lys  
785 790 795 800

Asp Ile Val Leu Arg Ala Ser Ser Glu Phe Lys Ser Val Leu Leu Ser  
805 810 815

Leu Arg Gln Gly Ser Leu Ile Glu Phe Ser Thr Ile Leu Glu Gly Arg  
820 825 830

Leu Gly Ser Lys Trp Pro Val Phe Glu Leu Lys Ala Ile Ser Cys Leu  
835 840 845

Asn Cys Met Ala Gln Leu Ser Pro Thr Arg Arg His Val Lys Ile Glu  
850 855 860

His Asp Trp Arg Ser Thr Val His Gly Ala Val Lys Phe Ala Phe Asp  
865 870 875 880

Phe Phe Phe Phe Pro Phe Leu Ser Ala Ala  
885 890

<210> 98  
<211> 528

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 98

Met Ala Glu His Leu Glu Leu Leu Ala Glu Met Pro Met Val Gly Arg  
 1 5 10 15

Met Ser Thr Gln Glu Arg Leu Lys His Ala Gln Lys Arg Arg Ala Gln  
 20 25 30

Gln Val Lys Met Trp Ala Gln Ala Glu Lys Glu Ala Gln Gly Lys Lys  
 35 40 45

Gly Pro Gly Glu Arg Pro Arg Lys Glu Ala Ala Ser Gln Gly Leu Leu  
 50 55 60

Lys Gln Val Leu Phe Pro Pro Ser Val Val Leu Leu Glu Ala Ala Ala  
 65 70 75 80

Arg Asn Asp Leu Glu Glu Val Arg Gln Phe Leu Gly Ser Gly Val Ser  
 85 90 95

Pro Asp Leu Ala Asn Glu Asp Gly Leu Thr Ala Leu His Gln Cys Cys  
 100 105 110

Ile Asp Asp Phe Arg Glu Met Val Gln Gln Leu Leu Glu Ala Gly Ala  
 115 120 125

Asn Ile Asn Ala Cys Asp Ser Glu Cys Trp Thr Pro Leu His Ala Ala  
 130 135 140

Ala Thr Cys Gly His Leu His Leu Val Glu Leu Leu Ile Ala Ser Gly  
 145 150 155 160

Ala Asn Leu Leu Ala Val Asn Thr Asp Gly Asn Met Pro Tyr Asp Leu  
 165 170 175

Cys Asp Asp Glu Gln Thr Leu Asp Cys Leu Glu Thr Ala Met Ala Asp  
 180 185 190

Arg Gly Ile Thr Gln Asp Ser Ile Glu Ala Ala Arg Ala Val Pro Glu  
 195 200 205

Leu Arg Met Leu Asp Asp Ile Arg Ser Arg Leu Gln Ala Gly Ala Asp  
 210 215 220

Leu His Ala Pro Leu Asp His Gly Ala Thr Leu Leu His Val Ala Ala



225	230	235	240
Ala Asn Gly Phe Ser Glu Ala Ala Ala Leu Leu Leu Glu His Arg Ala	245	250	255
Ser Leu Ser Ala Lys Asp Gln Asp Gly Trp Glu Pro Leu His Ala Ala	260	265	270
Ala Tyr Trp Gly Gln Val Pro Leu Val Glu Leu Leu Val Ala His Gly	275	280	285
Ala Asp Leu Asn Ala Lys Ser Leu Met Asp Glu Thr Pro Leu Asp Val	290	295	300
Cys Gly Asp Glu Glu Val Arg Ala Lys Leu Leu Glu Leu Lys His Lys	305	310	315
His Asp Ala Leu Leu Arg Ala Gln Ser Arg Gln Arg Ser Leu Leu Arg	325	330	335
Arg Arg Thr Ser Ser Ala Gly Ser Arg Gly Lys Val Val Arg Arg Val	340	345	350
Ser Leu Thr Gln Arg Thr Asp Leu Tyr Arg Lys Gln His Ala Gln Glu	355	360	365
Ala Ile Val Trp Gln Gln Pro Pro Pro Thr Ser Pro Glu Pro Pro Glu	370	375	380
Asp Asn Asp Asp Arg Gln Thr Gly Ala Glu Leu Arg Pro Pro Pro Pro	385	390	395
Glu Glu Asp Asn Pro Glu Val Val Arg Pro His Asn Gly Arg Val Gly	405	410	415
Gly Ser Pro Val Arg His Leu Tyr Ser Lys Arg Leu Asp Arg Ser Val	420	425	430
Ser Tyr Gln Leu Ser Pro Leu Asp Ser Thr Thr Pro His Thr Leu Val	435	440	445
His Asp Lys Ala His His Thr Leu Ala Asp Leu Lys Arg Gln Arg Ala	450	455	460
Ala Ala Lys Leu Gln Arg Pro Pro Pro Glu Gly Pro Glu Ser Pro Glu	465	470	475
			480

Thr Ala Glu Pro Gly Leu Pro Gly Asp Thr Val Thr Pro Gln Pro Asp  
 485 490 495

Cys Gly Phe Arg Ala Gly Gly Asp Pro Pro Leu Leu Lys Leu Thr Ala  
 500 505 510

Pro Ala Val Glu Ala Pro Val Glu Arg Arg Pro Cys Cys Leu Leu Met  
 515 520 525

<210> 99  
 <211> 567  
 <212> PRT  
 <213> Homo sapiens

<400> 99

Met Ala Ser His Val Asp Leu Leu Thr Glu Leu Gln Leu Leu Glu Lys  
 1 5 10 15

Val Pro Thr Leu Glu Arg Leu Arg Ala Ala Gln Lys Arg Arg Ala Gln  
 20 25 30

Gln Leu Lys Lys Trp Ala Gln Tyr Glu Gln Asp Leu Gln His Arg Lys  
 35 40 45

Arg Lys His Glu Arg Lys Arg Ser Thr Gly Gly Arg Arg Lys Lys Val  
 50 55 60

Ser Phe Glu Ala Ser Val Ala Leu Leu Glu Ala Ser Leu Arg Asn Asp  
 65 70 75 80

Ala Glu Glu Val Arg Tyr Phe Leu Lys Asn Lys Val Ser Pro Asp Leu  
 85 90 95

Cys Asn Glu Asp Gly Leu Thr Ala Leu His Gln Cys Cys Ile Asp Asn  
 100 105 110

Phe Glu Glu Ile Val Lys Leu Leu Leu Ser His Gly Ala Asn Val Asn  
 115 120 125

Ala Lys Asp Asn Glu Leu Trp Thr Pro Leu His Ala Ala Ala Thr Cys  
 130 135 140

Gly His Ile Asn Leu Val Lys Ile Leu Val Gln Tyr Gly Ala Asp Leu  
 145 150 155 160

Leu Ala Val Asn Ser Asp Gly Asn Met Pro Tyr Asp Leu Cys Glu Asp  
 165 170 175

Glu Pro Thr Leu Asp Val Ile Glu Thr Cys Met Ala Tyr Gln Gly Ile  
 180 185 190

Thr Gln Glu Lys Ile Asn Glu Met Arg Val Ala Pro Glu Gln Gln Met  
 195 200 205

Ile Ala Asp Ile His Cys Met Ile Ala Ala Gly Gln Asp Leu Asp Trp  
 210 215 220

Ile Asp Ala Gln Gly Ala Thr Leu Leu His Ile Ala Gly Ala Asn Gly  
 225 230 235 240

Tyr Leu Arg Ala Ala Glu Leu Leu Leu Asp His Gly Val Arg Val Asp  
 245 250 255

Val Lys Asp Trp Asp Gly Trp Glu Pro Leu His Ala Ala Ala Phe Trp  
 260 265 270

Gly Gln Met Gln Met Ala Glu Leu Leu Val Ser His Gly Ala Ser Leu  
 275 280 285

Ser Ala Arg Thr Ser Met Asp Glu Met Pro Ile Asp Leu Cys Glu Glu  
 290 295 300

Glu Glu Phe Lys Val Leu Leu Leu Glu Leu Lys His Lys His Asp Val  
 305 310 315 320

Ile Met Lys Ser Gln Leu Arg His Lys Ser Ser Leu Ser Arg Arg Thr  
 325 330 335

Ser Ser Ala Gly Ser Arg Gly Lys Val Val Arg Arg Ala Ser Leu Ser  
 340 345 350

Asp Arg Thr Asn Leu Tyr Arg Lys Glu Tyr Glu Gly Glu Ala Ile Leu  
 355 360 365

Trp Gln Arg Ser Ala Ala Glu Asp Gln Arg Thr Ser Thr Tyr Asn Gly  
 370 375 380

Asp Ile Arg Glu Thr Arg Thr Asp Gln Glu Asn Lys Asp Pro Asn Pro  
 385 390 395 400

Arg Leu Glu Lys Pro Val Leu Leu Ser Glu Phe Pro Thr Lys Ile Pro  
 405 410 415

Arg Gly Glu Leu Asp Met Pro Val Glu Asn Gly Leu Arg Ala Pro Val  
 420 425 430

Ser Ala Tyr Gln Tyr Ala Leu Ala Asn Gly Asp Val Trp Lys Val His  
 435 440 445

Glu Val Pro Asp Tyr Ser Met Ala Tyr Gly Asn Pro Gly Val Ala Asp  
 450 455 460

Ala Thr Pro Pro Trp Ser Ser Tyr Lys Glu Gln Ser Pro Gln Thr Leu  
 465 470 475 480

Leu Glu Leu Lys Arg Gln Arg Ala Ala Ala Lys Leu Leu Ser His Pro  
 485 490 495

Phe Leu Ser Thr His Leu Gly Ser Ser Met Ala Arg Thr Gly Glu Ser  
 500 505 510

Ser Ser Glu Gly Lys Ala Pro Leu Ile Gly Gly Arg Thr Ser Pro Tyr  
 515 520 525

Ser Ser Asn Gly Thr Ser Val Tyr Tyr Thr Val Thr Ser Gly Asp Pro  
 530 535 540

Pro Leu Leu Lys Phe Lys Ala Pro Ile Glu Glu Met Glu Glu Lys Val  
 545 550 555 560

His Gly Cys Cys Arg Ile Ser  
 565

<210> 100  
 <211> 380  
 <212> PRT  
 <213> Homo sapiens

<400> 100

Met Leu Arg Arg Lys Pro Ser Asn Ala Ser Glu Lys Glu Pro Thr Gln  
 1 5 10 15

Lys Lys Lys Leu Ser Leu Gln Arg Ser Ser Ser Phe Lys Asp Phe Ala  
 20 25 30

Lys Ser Lys Pro Ser Ser Pro Val Val Ser Glu Lys Glu Phe Asn Leu  
 35 40 45

Asp Asp Asn Ile Pro Glu Asp Asp Ser Gly Val Pro Thr Pro Glu Asp  
 50 55 60

Ala Gly Lys Ser Gly Lys Lys Leu Gly Lys Lys Trp Arg Ala Val Ile  
 65 70 75 80  
 Ser Arg Thr Met Asn Arg Lys Met Gly Lys Met Met Val Lys Ala Leu  
 85 90 95  
 Ser Glu Glu Met Ala Asp Thr Leu Glu Glu Gly Ser Ala Ser Pro Thr  
 100 105 110  
 Ser Pro Asp Tyr Ser Leu Asp Ser Pro Gly Pro Glu Lys Met Ala Leu  
 115 120 125  
 Ala Phe Ser Glu Gln Glu Glu His Glu Leu Pro Val Leu Ser Arg Gln  
 130 135 140  
 Ala Ser Thr Gly Ser Glu Leu Cys Ser Pro Ser Pro Gly Ser Gly Ser  
 145 150 155 160  
 Phe Gly Glu Glu Pro Pro Ala Pro Gln Tyr Thr Gly Pro Phe Cys Gly  
 165 170 175  
 Arg Ala Arg Val His Thr Asp Phe Thr Pro Ser Pro Tyr Asp His Asp  
 180 185 190  
 Ser Leu Lys Leu Gln Lys Gly Asp Val Ile Gln Ile Ile Glu Lys Pro  
 195 200 205  
 Pro Val Gly Thr Trp Leu Gly Leu Leu Asn Gly Lys Val Gly Ser Phe  
 210 215 220  
 Lys Phe Ile Tyr Val Asp Val Leu Pro Glu Glu Ala Val Gly His Ala  
 225 230 235 240  
 Arg Pro Ser Arg Arg Gln Ser Lys Gly Lys Arg Pro Lys Pro Lys Thr  
 245 250 255  
 Leu His Glu Leu Leu Glu Arg Ile Gly Leu Glu Glu His Thr Ser Thr  
 260 265 270  
 Leu Leu Leu Asn Gly Tyr Gln Thr Leu Glu Asp Phe Lys Glu Leu Arg  
 275 280 285  
 Glu Thr His Leu Asn Glu Leu Asn Ile Met Asp Pro Gln His Arg Ala  
 290 295 300  
 Lys Leu Leu Thr Ala Ala Glu Leu Leu Leu Asp Tyr Asp Thr Gly Ser



Gly Asp Trp Lys Lys Lys Asn Lys Tyr Phe Trp Gln Asn Phe Arg Lys  
 145 150 155 160

Asn Gln Lys Gly Ile Met Arg Gln Thr Ser Lys Gly Glu Asp Val Gly  
 165 170 175

Tyr Val Ala Ser Glu Ile Thr Met Ser Asp Glu Glu Arg Ile Gln Leu  
 180 185 190

Met Met Met Val Lys Glu Lys Met Ile Thr Ile Glu Glu Ala Leu Ala  
 195 200 205

Arg Leu Lys Glu Tyr Glu Ala Gln His Arg Gln Ser Ala Ala Leu Asp  
 210 215 220

Pro Ala Asp Trp Pro Asp Gly Ser Tyr Pro Thr Phe Asp Gly Ser Ser  
 225 230 235 240

Asn Cys Asn Ser Arg Glu Gln Ser Asp Asp Glu Thr Glu Glu Ser Val  
 245 250 255

Lys Phe Lys Arg Leu His Lys Leu Val Asn Ser Thr Arg Arg Val Arg  
 260 265 270

Lys Lys Leu Ile Arg Val Glu Glu Met Lys Lys Pro Ser Thr Glu Gly  
 275 280 285

Gly Glu Glu His Val Phe Glu Asn Ser Pro Val Leu Asp Glu Arg Ser  
 290 295 300

Ala Leu Tyr Ser Gly Val His Lys Lys Pro Leu Phe Phe Asp Gly Ser  
 305 310 315 320

Pro Glu Lys Pro Pro Glu Asp Asp Ser Asp Ser Leu Thr Thr Ser Pro  
 325 330 335

Ser Ser Ser Ser Leu Asp Thr Trp Gly Ala Gly Arg Lys Leu Val Lys  
 340 345 350

Thr Phe Ser Lys Gly Glu Ser Arg Gly Leu Ile Lys Pro Pro Lys Lys  
 355 360 365

Met Gly Thr Phe Phe Ser Tyr Pro Glu Glu Glu Lys Ala Gln Lys Val  
 370 375 380

Ser Arg Ser Leu Thr Glu Gly Glu Met Lys Lys Gly Leu Gly Ser Leu  
 385 390 395 400

Ser His Gly Arg Thr Cys Ser Phe Gly Gly Phe Asp Leu Thr Asn Arg  
 405 410 415

Ser Leu His Val Gly Ser Asn Asn Ser Asp Pro Met Gly Lys Glu Gly  
 420 425 430

Asp Phe Val Tyr Lys Glu Val Ile Lys Ser Pro Thr Ala Ser Arg Ile  
 435 440 445

Ser Leu Gly Lys Lys Val Lys Ser Val Lys Glu Thr Met Arg Lys Arg  
 450 455 460

Met Ser Lys Lys Tyr Ser Ser Ser Val Ser Glu Gln Asp Ser Gly Leu  
 465 470 475 480

Asp Gly Met Pro Gly Ser Pro Pro Pro Ser Gln Pro Asp Pro Glu His  
 485 490 495

Leu Asp Lys Pro Lys Leu Lys Ala Gly Gly Ser Val Glu Ser Leu Arg  
 500 505 510

Ser Ser Leu Ser Gly Gln Ser Ser Met Ser Gly Gln Thr Val Ser Thr  
 515 520 525

Thr Asp Ser Ser Thr Ser Asn Arg Glu Ser Val Lys Ser Glu Asp Gly  
 530 535 540

Asp Asp Glu Glu Pro Pro Tyr Arg Gly Pro Phe Cys Gly Arg Ala Arg  
 545 550 555 560

Val His Thr Asp Phe Thr Pro Ser Pro Tyr Asp Thr Asp Ser Leu Lys  
 565 570 575

Leu Lys Lys Gly Asp Ile Ile Asp Ile Ile Ser Lys Pro Pro Met Gly  
 580 585 590

Thr Trp Met Gly Leu Leu Asn Asn Lys Val Gly Thr Phe Lys Phe Ile  
 595 600 605

Tyr Val Asp Val Leu Ser Glu Asp Glu Glu Lys Pro Lys Arg Pro Thr  
 610 615 620

Arg Arg Arg Arg Lys Gly Arg Pro Pro Gln Pro Lys Ser Val Glu Asp  
 625 630 635 640



Leu Leu Asp Arg Ile Asn Leu Lys Glu His Met Pro Thr Phe Leu Phe  
645 650 655

Asn Gly Tyr Glu Asp Leu Asp Thr Phe Lys Leu Leu Glu Glu Glu Asp  
660 665 670

Leu Asp Glu Leu Asn Ile Arg Asp Pro Glu His Arg Ala Val Leu Leu  
675 680 685

Thr Ala Val Glu Leu Leu Gln Glu Tyr Asp Ser Asn Ser Asp Gln Ser  
690 695 700

Gly Ser Gln Glu Lys Leu Leu Val Asp Ser Gln Gly Leu Ser Gly Cys  
705 710 715 720

Ser Pro Arg Asp Ser Gly Cys Tyr Glu Ser Ser Glu Asn Leu Glu Asn  
725 730 735

Gly Lys Thr Arg Lys Ala Ser Leu Leu Ser Ala Lys Ser Ser Thr Glu  
740 745 750

Pro Ser Leu Lys Ser Phe Ser Arg Asn Gln Leu Gly Asn Tyr Pro Thr  
755 760 765

Leu Pro Leu Met Lys Ser Gly Asp Ala Leu Lys Gln Gly Gln Glu Glu  
770 775 780

Gly Arg Leu Gly Gly Gly Leu Ala Pro Asp Thr Ser Lys Ser Cys Asp  
785 790 795 800

Pro Pro Gly Val Thr Gly Leu Asn Lys Asn Arg Arg Ser Leu Pro Val  
805 810 815

Ser Ile Cys Arg Ser Cys Glu Thr Leu Glu Gly Pro Gln Thr Val Asp  
820 825 830

Thr Trp Pro Arg Ser His Ser Leu Asp Asp Leu Gln Val Glu Pro Gly  
835 840 845

Ala Glu Gln Asp Val Pro Thr Glu Val Thr Glu Pro Pro Pro Gln Ile  
850 855 860

Val Pro Glu Val Pro Gln Lys Thr Thr Ala Ser Ser Thr Lys Ala Gln  
865 870 875 880

Pro Leu Glu Gln Asp Ser Ala Val Asp Asn Ala Leu Leu Leu Thr Gln  
885 890 895

Ser Lys Arg Phe Ser Glu Pro Gln Lys Leu Thr Thr Lys Lys Leu Glu  
 900 905 910

Gly Ser Ile Ala Ala Ser Gly Arg Gly Leu Ser Pro Pro Gln Cys Leu  
 915 920 925

Pro Arg Asn Tyr Asp Ala Gln Pro Pro Gly Ala Lys His Gly Leu Ala  
 930 935 940

Arg Thr Pro Leu Glu Gly His Arg Lys Gly His Glu Phe Glu Gly Thr  
 945 950 955 960

His His Pro Leu Gly Thr Lys Glu Gly Val Asp Ala Glu Gln Arg Met  
 965 970 975

Gln Pro Lys Ile Pro Ser Gln Pro Pro Pro Val Pro Ala Lys Lys Ser  
 980 985 990

Arg Glu Arg Leu Ala Asn Gly Leu His Pro Val Pro Met Gly Pro Ser  
 995 1000 1005

Gly Ala Leu Pro Ser Pro Asp Ala Pro Cys Leu Pro Val Lys Arg  
 1010 1015 1020

Gly Ser Pro Ala Ser Pro Thr Ser Pro Ser Asp Cys Pro Pro Ala  
 1025 1030 1035

Leu Ala Pro Arg Pro Leu Ser Gly Gln Ala Pro Gly Ser Pro Pro  
 1040 1045 1050

Ser Thr Arg Pro Pro Pro Trp Leu Ser Glu Leu Pro Glu Asn Thr  
 1055 1060 1065

Ser Leu Gln Glu His Gly Val Lys Leu Gly Pro Ala Leu Thr Arg  
 1070 1075 1080

Lys Val Ser Cys Ala Arg Gly Val Asp Leu Glu Thr Leu Thr Glu  
 1085 1090 1095

Asn Lys Leu His Ala Glu Gly Ile Asp Leu Thr Glu Glu Pro Tyr  
 1100 1105 1110

Ser Asp Lys His Gly Arg Cys Gly Ile Pro Glu Ala Leu Val Gln  
 1115 1120 1125

Arg Tyr Ala Glu Asp Leu Asp Gln Pro Glu Arg Asp Val Ala Ala  
 1130 1135 1140  
 Asn Met Asp Gln Ile Arg Val Lys Gln Leu Arg Lys Gln His Arg  
 1145 1150 1155  
 Met Ala Ile Pro Ser Gly Gly Leu Thr Glu Ile Cys Arg Lys Pro  
 1160 1165 1170  
 Val Ser Pro Gly Cys Ile Ser Ser Val Ser Asp Trp Leu Ile Ser  
 1175 1180 1185  
 Ile Gly Leu Pro Met Tyr Ala Gly Thr Leu Ser Thr Ala Gly Phe  
 1190 1195 1200  
 Ser Thr Leu Ser Gln Val Pro Ser Leu Ser His Thr Cys Leu Gln  
 1205 1210 1215  
 Glu Ala Gly Ile Thr Glu Glu Arg His Ile Arg Lys Leu Leu Ser  
 1220 1225 1230  
 Ala Ala Arg Leu Phe Lys Leu Pro Pro Gly Pro Glu Ala Met  
 1235 1240 1245  
 <210> 102  
 <211> 373  
 <212> PRT  
 <213> Homo sapiens  
 <400> 102  
 Met Leu Lys Arg Lys Pro Ser Asn Val Ser Glu Lys Glu Lys His Gln  
 1 5 10 15  
 Lys Pro Lys Arg Ser Ser Ser Phe Gly Asn Phe Asp Arg Phe Arg Asn  
 20 25 30  
 Asn Ser Leu Ser Lys Pro Asp Asp Ser Thr Glu Ala His Glu Gly Asp  
 35 40 45  
 Pro Thr Asn Gly Ser Gly Glu Gln Ser Lys Thr Ser Asn Asn Gly Gly  
 50 55 60  
 Gly Leu Gly Lys Lys Met Arg Ala Ile Ser Trp Thr Met Lys Lys Lys  
 65 70 75 80  
 Val Gly Lys Lys Tyr Ile Lys Ala Leu Ser Glu Glu Lys Asp Glu Glu  
 85 90 95

Asp Gly Glu Asn Ala His Pro Tyr Arg Asn Ser Asp Pro Val Ile Gly  
 100 105 110  
 Thr His Thr Glu Lys Val Ser Leu Lys Ala Ser Asp Ser Met Asp Ser  
 115 120 125  
 Leu Tyr Ser Gly Gln Ser Ser Ser Ser Gly Ile Thr Ser Cys Ser Asp  
 130 135 140  
 Gly Thr Ser Asn Arg Asp Ser Phe Arg Leu Asp Asp Asp Gly Pro Tyr  
 145 150 155 160  
 Ser Gly Pro Phe Cys Gly Arg Ala Arg Val His Thr Asp Phe Thr Pro  
 165 170 175  
 Ser Pro Tyr Asp Thr Asp Ser Leu Lys Ile Lys Lys Gly Asp Ile Ile  
 180 185 190  
 Asp Ile Ile Cys Lys Thr Pro Met Gly Met Trp Thr Gly Met Leu Asn  
 195 200 205  
 Asn Lys Val Gly Asn Phe Lys Phe Ile Tyr Val Asp Val Ile Ser Glu  
 210 215 220  
 Glu Glu Ala Ala Pro Lys Lys Ile Lys Ala Asn Arg Arg Ser Asn Ser  
 225 230 235 240  
 Lys Lys Ser Lys Thr Leu Gln Glu Phe Leu Glu Arg Ile His Leu Gln  
 245 250 255  
 Glu Tyr Thr Ser Thr Leu Leu Leu Asn Gly Tyr Glu Thr Leu Glu Asp  
 260 265 270  
 Leu Lys Asp Ile Lys Glu Ser His Leu Ile Glu Leu Asn Ile Glu Asn  
 275 280 285  
 Pro Asp Asp Arg Arg Arg Leu Leu Ser Ala Ala Glu Asn Phe Leu Glu  
 290 295 300  
 Glu Glu Ile Ile Gln Glu Gln Glu Asn Glu Pro Glu Pro Leu Ser Leu  
 305 310 315 320  
 Ser Ser Asp Ile Ser Leu Asn Lys Ser Gln Leu Asp Asp Cys Pro Arg  
 325 330 335  
 Asp Ser Gly Cys Tyr Ile Ser Ser Gly Asn Ser Asp Asn Gly Lys Glu

340 345 350  
 Asp Leu Glu Ser Glu Asn Leu Ser Asp Met Val His Lys Ile Ile Ile  
 355 360 365  
 Thr Glu Pro Ser Asp  
 370  
 <210> 103  
 <211> 431  
 <212> PRT  
 <213> Homo sapiens  
 <400> 103  
 Met Glu Gly Ser Ala Ser Pro Pro Glu Lys Pro Arg Ala Arg Pro Ala  
 1 5 10 15  
 Ala Ala Val Leu Cys Arg Gly Pro Val Glu Pro Leu Val Phe Leu Ala  
 20 25 30  
 Asn Phe Ala Leu Val Leu Gln Gly Pro Leu Thr Thr Gln Tyr Leu Trp  
 35 40 45  
 His Arg Phe Ser Ala Asp Leu Gly Tyr Asn Gly Thr Arg Gln Arg Gly  
 50 55 60  
 Gly Cys Ser Asn Arg Ser Ala Asp Pro Thr Met Gln Glu Val Glu Thr  
 65 70 75 80  
 Leu Thr Ser His Trp Thr Leu Tyr Met Asn Val Gly Gly Phe Leu Val  
 85 90 95  
 Gly Leu Phe Ser Ser Thr Leu Leu Gly Ala Trp Ser Asp Ser Val Gly  
 100 105 110  
 Arg Arg Pro Leu Leu Val Leu Ala Ser Leu Gly Leu Leu Leu Gln Ala  
 115 120 125  
 Leu Val Ser Val Phe Val Val Gln Leu Gln Leu His Val Gly Tyr Phe  
 130 135 140  
 Val Leu Gly Arg Ile Leu Cys Ala Leu Leu Gly Asp Phe Gly Gly Leu  
 145 150 155 160  
 Leu Ala Ala Ser Phe Ala Ser Val Ala Asp Val Ser Ser Ser Arg Ser  
 165 170 175

Arg Thr Phe Arg Met Ala Leu Leu Glu Ala Ser Ile Gly Val Ala Gly  
 180 185 190

Met Leu Ala Ser Leu Leu Gly Gly His Trp Leu Arg Ala Gln Gly Tyr  
 195 200 205

Ala Asn Pro Phe Trp Leu Ala Leu Ala Leu Leu Ile Ala Met Thr Leu  
 210 215 220

Tyr Ala Ala Phe Cys Phe Gly Glu Thr Leu Lys Glu Pro Lys Ser Thr  
 225 230 235 240

Arg Leu Phe Thr Phe Arg His His Arg Ser Ile Val Gln Leu Tyr Val  
 245 250 255

Ala Pro Ala Pro Glu Lys Ser Arg Lys His Leu Ala Leu Tyr Ser Leu  
 260 265 270

Ala Ile Phe Val Val Ile Thr Val His Phe Gly Ala Gln Asp Ile Leu  
 275 280 285

Thr Leu Tyr Glu Leu Ser Thr Pro Leu Cys Trp Asp Ser Lys Leu Ile  
 290 295 300

Gly Tyr Gly Ser Ala Ala Gln His Leu Pro Tyr Leu Thr Ser Leu Leu  
 305 310 315 320

Ala Leu Lys Leu Leu Gln Tyr Cys Leu Ala Asp Ala Trp Val Ala Glu  
 325 330 335

Ile Gly Leu Ala Phe Asn Ile Leu Gly Met Val Val Phe Ala Phe Ala  
 340 345 350

Thr Ile Thr Pro Leu Met Phe Thr Gly Ala Leu Phe Ser Ala Val Ala  
 355 360 365

Cys Val Asn Ser Leu Ala Met Leu Thr Ala Ser Gly Ile Phe Asn Ser  
 370 375 380

Leu Tyr Pro Ala Thr Leu Asn Phe Met Lys Gly Phe Pro Phe Leu Leu  
 385 390 395 400

Gly Ala Gly Leu Leu Leu Ile Pro Ala Val Leu Ile Gly Met Leu Glu  
 405 410 415

Lys Ala Asp Pro His Leu Glu Phe Gln Gln Phe Pro Gln Ser Pro  
 420 425 430

<210> 104  
 <211> 463  
 <212> PRT  
 <213> Homo sapiens

<400> 104

Met Lys Ile Leu Phe Val Glu Pro Ala Ile Phe Leu Ser Ala Phe Ala  
 1 5 10 15

Met Thr Leu Thr Gly Pro Leu Thr Thr Gln Tyr Val Tyr Arg Arg Ile  
 20 25 30

Trp Glu Glu Thr Gly Asn Tyr Thr Phe Ser Ser Asp Ser Asn Ile Ser  
 35 40 45

Glu Cys Glu Lys Asn Lys Ser Ser Pro Ile Phe Ala Phe Gln Glu Glu  
 50 55 60

Val Gln Lys Lys Val Ser Arg Phe Asn Leu Gln Met Asp Ile Ser Gly  
 65 70 75 80

Leu Ile Pro Gly Leu Val Ser Thr Phe Ile Leu Leu Ser Ile Ser Asp  
 85 90 95

His Tyr Gly Arg Lys Phe Pro Met Ile Leu Ser Ser Val Gly Ala Leu  
 100 105 110

Ala Thr Ser Val Trp Leu Cys Leu Leu Cys Tyr Phe Ala Leu Pro Phe  
 115 120 125

Gln Leu Leu Ile Ala Ser Thr Phe Ile Gly Ala Ile Cys Gly Asn Tyr  
 130 135 140

Thr Thr Phe Trp Gly Ala Cys Phe Ala Tyr Ile Val Asp Gln Cys Lys  
 145 150 155 160

Glu His Lys Gln Lys Thr Ile Arg Ile Ala Ile Ile Asp Phe Leu Leu  
 165 170 175

Gly Leu Val Thr Gly Leu Thr Gly Leu Ser Ser Gly Tyr Phe Ile Arg  
 180 185 190

Glu Leu Gly Phe Glu Trp Ser Phe Leu Ile Ile Ala Val Ser Leu Ala  
 195 200 205

Val Asn Leu Ile Tyr Ile Leu Phe Phe Leu Gly Asp Pro Val Lys Glu

[illegible]



<210> 105  
 <211> 575  
 <212> PRT  
 <213> Homo sapiens

<400> 105

Met Ser Ala Ala Thr His Ser Pro Met Met Gln Val Ala Ser Gly Asn  
 1 5 10 15

Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp Glu Ile Lys Ile Asp Pro  
 20 25 30

Gln Thr Gly Trp Pro Phe Phe Val Asp His Asn Ser Arg Thr Thr Thr  
 35 40 45

Trp Asn Asp Pro Arg Val Pro Ser Glu Gly Pro Lys Glu Thr Pro Ser  
 50 55 60

Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser Arg Leu Pro Pro Ala Arg  
 65 70 75 80

Glu Gly His Pro Val Tyr Pro Gln Leu Arg Pro Gly Tyr Ile Pro Ile  
 85 90 95

Pro Val Leu His Glu Gly Ala Glu Asn Arg Gln Val His Pro Phe His  
 100 105 110

Val Tyr Pro Gln Pro Gly Met Gln Arg Phe Arg Thr Glu Ala Ala Ala  
 115 120 125

Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu Arg Gly Met Pro Glu Thr  
 130 135 140

Thr Gln Pro Asp Lys Gln Cys Gly Gln Val Ala Ala Ala Ala Ala Ala  
 145 150 155 160

Gln Pro Pro Ala Ser His Gly Pro Glu Arg Ser Gln Ser Pro Ala Ala  
 165 170 175

Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala Ser Leu Pro Ser Ser Gly  
 180 185 190

Arg Ser Ser Leu Gly Ser His Gln Leu Pro Arg Gly Tyr Ile Ser Ile  
 195 200 205

Pro Val Ile His Glu Gln Asn Val Thr Arg Pro Ala Ala Gln Pro Ser  
 210 215 220

Phe His Gln Ala Gln Lys Thr His Tyr Pro Ala Gln Gln Gly Glu Tyr  
 225 230 235 240

Gln Thr His Gln Pro Val Tyr His Lys Ile Gln Gly Asp Asp Trp Glu  
 245 250 255

Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe Arg Ser Ser Val Gln Gly  
 260 265 270

Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg Ser Ser Thr Pro Leu His  
 275 280 285

Ser Pro Ser Pro Ile Arg Val His Thr Val Val Asp Arg Pro Gln Gln  
 290 295 300

Pro Met Thr His Arg Glu Thr Ala Pro Val Ser Gln Pro Glu Asn Lys  
 305 310 315 320

Pro Glu Ser Lys Pro Gly Pro Val Gly Pro Glu Leu Pro Pro Gly His  
 325 330 335

Ile Pro Ile Gln Val Ile Arg Lys Glu Val Asp Ser Lys Pro Val Ser  
 340 345 350

Gln Lys Pro Pro Pro Ser Glu Lys Val Glu Val Lys Val Pro Pro  
 355 360 365

Ala Pro Val Pro Cys Pro Pro Pro Ser Pro Gly Pro Ser Ala Val Pro  
 370 375 380

Ser Ser Pro Lys Ser Val Ala Thr Glu Glu Arg Ala Ala Pro Ser Thr  
 385 390 395 400

Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro Gly Glu Ala Glu Ala Pro  
 405 410 415

Pro Lys His Pro Gly Val Leu Lys Val Glu Ala Ile Leu Glu Lys Val  
 420 425 430

Gln Gly Leu Glu Gln Ala Val Asp Asn Phe Glu Gly Lys Lys Thr Asp  
 435 440 445

Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu Thr Lys Glu Leu Leu Ala  
 450 455 460

Leu Asp Ser Val Asp Pro Glu Gly Arg Ala Asp Val Arg Gln Ala Arg  
 465 470 475 480

Arg Asp Gly Val Arg Lys Val Gln Thr Ile Leu Glu Lys Leu Glu Gln  
 485 490 495

Lys Ala Ile Asp Val Pro Gly Gln Val Gln Val Tyr Glu Leu Gln Pro  
 500 505 510

Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln Ala Ile Met Glu Met Gly  
 515 520 525

Ala Val Ala Ala Asp Lys Gly Lys Lys Asn Ala Gly Asn Ala Glu Asp  
 530 535 540

Pro His Thr Glu Thr Gln Gln Pro Glu Ala Thr Ala Ala Ala Thr Ser  
 545 550 555 560

Asn Pro Ser Ser Met Thr Asp Thr Pro Gly Asn Pro Ala Ala Pro  
 565 570 575

<210> 106

<211> 457

<212> PRT

<213> Homo sapiens

<400> 106

Met Ser Ala Leu Arg Arg Ser Gly Tyr Gly Pro Ser Asp Gly Pro Ser  
 1 5 10 15

Tyr Gly Arg Tyr Tyr Gly Pro Gly Gly Gly Asp Val Pro Val His Pro  
 20 25 30

Pro Pro Pro Leu Tyr Pro Leu Arg Pro Glu Pro Pro Gln Pro Pro Ile  
 35 40 45

Ser Trp Arg Val Arg Gly Gly Gly Pro Ala Glu Thr Thr Trp Leu Gly  
 50 55 60

Glu Gly Gly Gly Gly Asp Gly Tyr Tyr Pro Ser Gly Gly Ala Trp Pro  
 65 70 75 80

Glu Pro Gly Arg Ala Gly Gly Ser His Gln Glu Gln Pro Pro Tyr Pro  
 85 90 95

Ser Tyr Asn Ser Asn Tyr Trp Asn Ser Thr Ala Arg Ser Arg Ala Pro  
 100 105 110

Tyr Pro Ser Thr Tyr Pro Val Arg Pro Glu Leu Gln Gly Gln Ser Leu  
 115 120 125

Asn Ser Tyr Thr Asn Gly Ala Tyr Gly Pro Thr Tyr Pro Pro Gly Pro  
 130 135 140

Gly Ala Asn Thr Ala Ser Tyr Ser Gly Ala Tyr Tyr Ala Pro Gly Tyr  
 145 150 155 160

Thr Gln Thr Ser Tyr Ser Thr Glu Val Pro Ser Thr Tyr Arg Ser Ser  
 165 170 175

Gly Asn Ser Pro Thr Pro Val Ser Arg Trp Ile Tyr Pro Gln Gln Asp  
 180 185 190

Cys Gln Thr Glu Ala Pro Pro Leu Arg Gly Gln Val Pro Gly Tyr Pro  
 195 200 205

Pro Ser Gln Asn Pro Gly Met Thr Leu Pro His Tyr Pro Tyr Gly Asp  
 210 215 220

Gly Asn Arg Ser Val Pro Gln Ser Gly Pro Thr Val Arg Pro Gln Glu  
 225 230 235 240

Asp Ala Trp Ala Ser Pro Gly Ala Tyr Gly Met Gly Gly Arg Tyr Pro  
 245 250 255

Trp Pro Ser Ser Ala Pro Ser Ala Pro Pro Gly Asn Leu Tyr Met Thr  
 260 265 270

Glu Ser Thr Ser Pro Trp Pro Ser Ser Gly Ser Pro Gln Ser Pro Pro  
 275 280 285

Ser Pro Pro Val Gln Gln Pro Lys Asp Ser Ser Tyr Pro Tyr Ser Gln  
 290 295 300

Ser Asp Gln Ser Met Asn Arg His Asn Phe Pro Cys Ser Val His Gln  
 305 310 315 320

Tyr Glu Ser Ser Gly Thr Val Asn Asn Asp Asp Ser Asp Leu Leu Asp  
 325 330 335

Ser Gln Val Gln Tyr Ser Ala Glu Pro Gln Leu Tyr Gly Asn Ala Thr  
 340 345 350

Ser Asp His Pro Asn Asn Gln Asp Gln Ser Ser Ser Leu Pro Glu Glu

355                                      360                                      365  
 Cys Val Pro Ser Asp Glu Ser Thr Pro Pro Ser Ile Lys Lys Ile Ile  
 370                                      375                                      380  
 His Val Leu Glu Lys Val Gln Tyr Leu Glu Gln Glu Val Glu Glu Phe  
 385                                      390                                      395                                      400  
 Val Gly Lys Lys Thr Asp Lys Ala Tyr Trp Leu Leu Glu Glu Met Leu  
 405                                      410                                      415  
 Thr Lys Glu Leu Leu Glu Leu Asp Ser Val Glu Thr Gly Gly Gln Asp  
 420                                      425                                      430  
 Ser Val Arg Gln Ala Arg Lys Glu Ala Val Cys Lys Ile Gln Ala Ile  
 435                                      440                                      445  
 Leu Glu Lys Leu Glu Lys Lys Gly Leu  
 450                                      455  
 <210> 107  
 <211> 373  
 <212> PRT  
 <213> Homo sapiens  
 .  
 <400> 107  
 Met Ala Gln Gly Arg Glu Arg Asp Glu Gly Pro His Ser Ala Gly Gly  
 1                                      5                                      10                                      15  
 Ala Ser Leu Ser Val Arg Trp Val Gln Gly Phe Pro Lys Gln Asn Val  
 20                                      25                                      30  
 His Phe Val Asn Asp Asn Thr Ile Cys Tyr Pro Cys Gly Asn Tyr Val  
 35                                      40                                      45  
 Ile Phe Ile Asn Ile Glu Thr Lys Lys Lys Thr Val Leu Gln Cys Ser  
 50                                      55                                      60  
 Asn Gly Ile Val Gly Val Met Ala Thr Asn Ile Pro Cys Glu Val Val  
 65                                      70                                      75                                      80  
 Ala Phe Ser Asp Arg Lys Leu Lys Pro Leu Ile Tyr Val Tyr Ser Phe  
 85                                      90                                      95  
 Pro Gly Leu Thr Arg Arg Thr Lys Leu Lys Gly Asn Ile Leu Leu Asp  
 100                                      105                                      110

Tyr Thr Leu Leu Ser Phe Ser Tyr Cys Gly Thr Tyr Leu Ala Ser Tyr  
 115 120 125

Ser Ser Leu Pro Glu Phe Glu Leu Ala Leu Trp Asn Trp Glu Ser Ser  
 130 135 140

Ile Ile Leu Cys Lys Lys Ser Gln Pro Gly Met Asp Val Asn Glu Met  
 145 150 155 160

Ser Phe Asn Pro Met Asn Trp Arg Gln Leu Cys Leu Ser Ser Pro Ser  
 165 170 175

Thr Val Ser Val Trp Thr Ile Glu Arg Ser Asn Gln Glu His Cys Phe  
 180 185 190

Arg Ala Arg Ser Val Lys Leu Pro Leu Glu Asp Gly Ser Phe Phe Asn  
 195 200 205

Glu Thr Asp Val Val Phe Pro Gln Ser Leu Pro Lys Asp Leu Ile Tyr  
 210 215 220

Gly Pro Val Leu Pro Leu Ser Ala Ile Ala Gly Leu Val Gly Lys Glu  
 225 230 235 240

Ala Glu Thr Phe Arg Pro Lys Asp Asp Leu Tyr Pro Leu Leu His Pro  
 245 250 255

Thr Met His Cys Trp Thr Pro Thr Ser Asp Leu Tyr Ile Gly Cys Glu  
 260 265 270

Glu Gly His Leu Leu Met Ile Asn Gly Asp Thr Leu Gln Val Thr Val  
 275 280 285

Leu Asn Lys Ile Glu Glu Glu Ser Pro Leu Glu Asp Arg Arg Asn Phe  
 290 295 300

Ile Ser Pro Val Thr Leu Val Tyr Gln Lys Glu Gly Val Leu Ala Ser  
 305 310 315 320

Gly Ile Asp Gly Phe Val Tyr Ser Phe Ile Ile Lys Asp Arg Ser Tyr  
 325 330 335

Met Ile Glu Asp Phe Leu Glu Ile Glu Arg Pro Val Glu His Met Thr  
 340 345 350

Phe Ser Pro Asn Tyr Thr Val Leu Leu Ile Gln Thr Asp Lys Val Cys  
 355 360 365

Trp Met Val Ile Ser  
370

<210> 108  
<211> 401  
<212> PRT  
<213> Homo sapiens

<400> 108

Met Lys Leu Ser Asp Leu His His Val Thr Leu Phe Gln Glu Ile Leu  
1 5 10 15

Leu Leu Lys Asn Phe Glu Lys Gln Glu Asn Ile Leu Gln Glu Arg Val  
20 25 30

Asn Ser Leu Asp Lys Glu Glu Gln Tyr Met Gln Trp Lys Ile Asn Glu  
35 40 45

Thr Leu Lys Glu Met Glu Glu Lys Lys Asn Glu Ile Thr Lys Leu Gln  
50 55 60

Glu Gln Glu Lys Ala Leu Tyr Ala Gly Phe Gln Ala Ala Ile Gly Glu  
65 70 75 80

Asn Asn Lys Phe Ala Asn Phe Leu Met Lys Val Leu Lys Lys Arg Ile  
85 90 95

Lys Arg Val Lys Lys Lys Glu Val Glu Gly Asp Ala Asp Glu Asp Glu  
100 105 110

Glu Ser Glu Glu Ser Ser Glu Glu Glu Ser Ser Leu Glu Ser Asp Glu  
115 120 125

Asp Glu Ser Glu Ser Glu Asp Glu Val Phe Asp Asp Ser Ile Cys Pro  
130 135 140

Thr Asn Cys Asp Val Ala Leu Phe Glu Leu Ala Leu His Leu Arg Glu  
145 150 155 160

Lys Arg Leu Asp Ile Glu Glu Ala Leu Val Glu Glu Lys Lys Ile Val  
165 170 175

Asp Asn Leu Lys Lys Glu Tyr Asp Thr Leu Ser Lys Lys Val Lys Ile  
180 185 190

Val Ala Thr Asn Leu Asn Ala Ala Glu Glu Ala Leu Glu Ala Tyr Gln

195	200	205
Arg Glu Lys Gln Gln Arg Leu Asn Glu Leu Leu Val Val Ile Pro Leu		
210	215	220
Lys Leu His Gln Ile Glu Tyr Val Val Phe Gly Glu Ile Pro Ser Asp		
225	230	235 240
Leu Ser Gly Thr Leu Val Phe Ser Asn His Ala Leu Arg Arg Leu Gln		
	245	250 255
Glu Arg Ile Arg Glu Leu Gln Glu Glu Asn Ser Lys Gln Gln Lys Leu		
	260	265 270
Asn Lys Glu Trp Arg Glu Arg Arg Lys Gln Leu Ile Arg Glu Lys Arg		
	275	280 285
Glu Met Thr Lys Thr Ile His Lys Met Glu Glu Thr Val Arg Gln Leu		
	290	295 300
Met Ile Ser Lys Phe Gly Arg Val Val Asn Leu Glu Ala Leu Gln Thr		
305	310	315 320
Leu Ser Val Asn Thr Thr Leu Glu Glu Leu Lys Ile Arg Lys Leu Arg		
	325	330 335
Lys Glu Leu Ala Asn Ala Lys Glu Met Lys Met Trp Glu Glu Lys Ile		
	340	345 350
Ala Gln Met Arg Trp Glu Leu Met Met Lys Thr Lys Glu His Thr Arg		
	355	360 365
Lys Leu Tyr Gln Met Asn Asp Leu Cys Ile Glu Lys Lys Lys Leu Asp		
	370	375 380
Ser Arg Leu Asn Thr Leu Gln Asn Gln Gln Asn Pro Gly Asn Gly Leu		
385	390	395 400

Ser

<210> 109  
 <211> 1674  
 <212> PRT  
 <213> Homo sapiens  
 <400> 109



Met Glu Asp Ala Ser Glu Ser Ser Arg Gly Val Ala Pro Leu Ile Asn  
1 5 10 15

Asn Val Val Leu Pro Gly Ser Pro Leu Ser Leu Pro Val Ser Val Thr  
20 25 30

Gly Cys Lys Ser His Arg Val Ala Asn Lys Lys Val Glu Ala Arg Ser  
35 40 45

Glu Lys Leu Leu Pro Thr Ala Leu Pro Pro Ser Glu Pro Lys Val Asp  
50 55 60

Gln Lys Leu Pro Arg Ser Ser Glu Arg Arg Gly Ser Gly Gly Gly Thr  
65 70 75 80

Gln Phe Pro Ala Arg Ser Arg Ala Val Ala Ala Gly Glu Ala Ala Ala  
85 90 95

Arg Gly Ala Ala Gly Pro Glu Arg Gly Ser Pro Leu Gly Arg Arg Val  
100 105 110

Ser Pro Arg Cys Leu Cys Ser Gly Glu Gly Gly Gln Val Ala Val Gly  
115 120 125

Val Ile Ala Gly Lys Arg Gly Arg Arg Gly Arg Asp Gly Ser Arg Arg  
130 135 140

Ala Pro Gly Gly Arg Glu Met Pro Leu Leu His Arg Lys Pro Phe Val  
145 150 155 160

Arg Gln Lys Pro Pro Ala Asp Leu Arg Pro Asp Glu Glu Val Phe Tyr  
165 170 175

Cys Lys Val Thr Asn Glu Ile Phe Arg His Tyr Asp Asp Phe Phe Glu  
180 185 190

Arg Thr Ile Leu Cys Asn Ser Leu Val Trp Ser Cys Ala Val Thr Gly  
195 200 205

Arg Pro Gly Leu Thr Tyr Gln Glu Ala Leu Glu Ser Glu Lys Lys Ala  
210 215 220

Arg Gln Asn Leu Gln Ser Phe Pro Glu Pro Leu Ile Ile Pro Val Leu  
225 230 235 240

Tyr Leu Thr Ser Leu Thr His Arg Ser Arg Leu His Glu Ile Cys Asp  
245 250 255

Asp Ile Phe Ala Tyr Val Lys Asp Arg Tyr Phe Val Glu Glu Thr Val  
 260 265 270

Glu Val Ile Arg Asn Asn Gly Ala Arg Leu Gln Cys Thr Ile Leu Glu  
 275 280 285

Val Leu Pro Pro Ser His Gln Asn Gly Phe Ala Asn Gly His Val Asn  
 290 295 300

Ser Val Asp Gly Glu Thr Ile Ile Ile Ser Asp Ser Asp Asp Ser Glu  
 305 310 315 320

Thr Gln Ser Cys Ser Phe Gln Asn Gly Lys Lys Lys Asp Ala Ile Asp  
 325 330 335

Pro Leu Leu Phe Lys Tyr Lys Val Gln Pro Thr Lys Lys Glu Leu His  
 340 345 350

Glu Ser Ala Ile Val Lys Ala Thr Gln Ile Ser Arg Arg Lys His Leu  
 355 360 365

Phe Ser Arg Asp Lys Leu Lys Leu Phe Leu Lys Gln His Cys Glu Pro  
 370 375 380

Gln Glu Gly Val Ile Lys Ile Lys Ala Ser Ser Leu Ser Thr Tyr Lys  
 385 390 395 400

Ile Ala Glu Gln Asp Phe Ser Tyr Phe Phe Pro Asp Asp Pro Pro Thr  
 405 410 415

Phe Ile Phe Ser Pro Ala Asn Arg Arg Arg Gly Arg Pro Pro Lys Arg  
 420 425 430

Ile His Ile Ser Gln Glu Asp Asn Val Ala Asn Lys Gln Thr Leu Ala  
 435 440 445

Ser Tyr Arg Ser Lys Ala Thr Lys Glu Arg Asp Lys Leu Leu Lys Gln  
 450 455 460

Glu Glu Met Lys Ser Leu Ala Phe Glu Lys Ala Lys Leu Lys Arg Glu  
 465 470 475 480

Lys Ala Asp Ala Leu Glu Ala Lys Lys Lys Glu Lys Glu Asp Lys Glu  
 485 490 495

Lys Lys Arg Glu Glu Leu Lys Lys Ile Val Glu Glu Glu Arg Leu Lys  
 500 505 510

Lys Lys Glu Glu Lys Glu Arg Leu Lys Val Glu Arg Glu Lys Glu Arg  
 515 520 525

Glu Lys Leu Arg Glu Glu Lys Arg Lys Tyr Val Glu Tyr Leu Lys Gln  
 530 535 540

Trp Ser Lys Pro Arg Glu Asp Met Glu Cys Asp Asp Leu Lys Glu Leu  
 545 550 555 560

Pro Glu Pro Thr Pro Val Lys Thr Arg Leu Pro Pro Glu Ile Phe Gly  
 565 570 575

Asp Ala Leu Met Val Leu Glu Phe Leu Asn Ala Phe Gly Glu Leu Phe  
 580 585 590

Asp Leu Gln Asp Glu Phe Pro Asp Gly Val Thr Leu Glu Val Leu Glu  
 595 600 605

Glu Ala Leu Val Gly Asn Asp Ser Glu Gly Pro Leu Cys Glu Leu Leu  
 610 615 620

Phe Phe Phe Leu Thr Ala Ile Phe Gln Ala Ile Ala Glu Glu Glu Glu  
 625 630 635 640

Glu Val Ala Lys Glu Gln Leu Thr Asp Ala Asp Thr Lys Gly Cys Ser  
 645 650 655

Leu Lys Ser Leu Asp Leu Asp Ser Cys Thr Leu Ser Glu Ile Leu Arg  
 660 665 670

Leu His Ile Leu Ala Ser Gly Ala Asp Val Thr Ser Ala Asn Ala Lys  
 675 680 685

Tyr Arg Tyr Gln Lys Arg Gly Gly Phe Asp Ala Thr Asp Asp Ala Cys  
 690 695 700

Met Glu Leu Arg Leu Ser Asn Pro Ser Leu Val Lys Lys Leu Ser Ser  
 705 710 715 720

Thr Ser Val Tyr Asp Leu Thr Pro Gly Glu Lys Met Lys Ile Leu His  
 725 730 735

Ala Leu Cys Gly Lys Leu Leu Thr Leu Val Ser Thr Arg Asp Phe Ile  
 740 745 750

Glu Asp Tyr Val Asp Ile Leu Arg Gln Ala Lys Gln Glu Phe Arg Glu  
755 760 765

Leu Lys Ala Glu Gln His Arg Lys Glu Arg Glu Glu Ala Ala Ala Arg  
770 775 780

Ile Arg Lys Arg Lys Glu Glu Lys Leu Lys Glu Gln Glu Gln Lys Met  
785 790 795 800

Lys Glu Lys Gln Glu Lys Leu Lys Glu Asp Glu Gln Arg Asn Ser Thr  
805 810 815

Ala Asp Ile Ser Ile Gly Glu Glu Glu Arg Glu Asp Phe Asp Thr Ser  
820 825 830

Ile Glu Ser Lys Asp Thr Glu Gln Lys Glu Leu Asp Gln Asp Met Phe  
835 840 845

Thr Glu Asp Glu Asp Asp Pro Gly Ser His Lys Arg Gly Arg Arg Gly  
850 855 860

Lys Arg Gly Gln Asn Gly Phe Lys Glu Phe Thr Arg Gln Glu Gln Ile  
865 870 875 880

Asn Cys Val Thr Arg Glu Leu Leu Thr Ala Asp Glu Glu Glu Ala Leu  
885 890 895

Lys Gln Glu His Gln Arg Lys Glu Lys Glu Leu Leu Glu Lys Ile Gln  
900 905 910

Ser Ala Ile Ala Cys Thr Asn Ile Phe Pro Leu Gly Arg Asp Arg Met  
915 920 925

Tyr Arg Arg Tyr Trp Ile Phe Pro Ser Ile Pro Gly Leu Phe Ile Glu  
930 935 940

Glu Asp Tyr Ser Gly Leu Thr Glu Asp Met Leu Leu Pro Arg Pro Ser  
945 950 955 960

Ser Phe Gln Asn Asn Val Gln Ser Gln Asp Pro Gln Val Ser Thr Lys  
965 970 975

Thr Gly Glu Pro Leu Met Ser Glu Ser Thr Ser Asn Ile Asp Gln Gly  
980 985 990

Pro	Arg	Asp	His	Ser	Val	Gln	Leu	Pro	Lys	Pro	Val	His	Lys	Pro	Asn
		995					1000						1005		
Arg	Trp	Cys	Phe	Tyr	Ser	Ser	Cys	Glu	Gln	Leu	Asp	Gln	Leu	Ile	
	1010					1015					1020				
Glu	Ala	Leu	Asn	Ser	Arg	Gly	His	Arg	Glu	Ser	Ala	Leu	Lys	Glu	
	1025					1030					1035				
Thr	Leu	Leu	Gln	Glu	Lys	Ser	Arg	Ile	Cys	Ala	Gln	Leu	Ala	Arg	
	1040					1045					1050				
Phe	Ser	Glu	Glu	Lys	Phe	His	Phe	Ser	Asp	Lys	Pro	Gln	Pro	Asp	
	1055					1060					1065				
Ser	Lys	Pro	Thr	Tyr	Ser	Arg	Gly	Arg	Ser	Ser	Asn	Ala	Tyr	Asp	
	1070					1075					1080				
Pro	Ser	Gln	Met	Cys	Ala	Glu	Lys	Gln	Leu	Glu	Leu	Arg	Leu	Arg	
	1085					1090					1095				
Asp	Phe	Leu	Leu	Asp	Ile	Glu	Asp	Arg	Ile	Tyr	Gln	Gly	Thr	Leu	
	1100					1105					1110				
Gly	Ala	Ile	Lys	Val	Thr	Asp	Arg	His	Ile	Trp	Arg	Ser	Ala	Leu	
	1115					1120					1125				
Glu	Ser	Gly	Arg	Tyr	Glu	Leu	Leu	Ser	Glu	Glu	Asn	Lys	Glu	Asn	
	1130					1135					1140				
Gly	Ile	Ile	Lys	Thr	Val	Asn	Glu	Asp	Val	Glu	Glu	Met	Glu	Ile	
	1145					1150					1155				
Asp	Glu	Gln	Thr	Lys	Val	Ile	Val	Lys	Asp	Arg	Leu	Leu	Gly	Ile	
	1160					1165					1170				
Lys	Thr	Glu	Thr	Pro	Ser	Thr	Val	Ser	Thr	Asn	Ala	Ser	Thr	Pro	
	1175					1180					1185				
Gln	Ser	Val	Ser	Ser	Val	Val	His	Tyr	Leu	Ala	Met	Ala	Leu	Phe	
	1190					1195					1200				
Gln	Ile	Glu	Gln	Gly	Ile	Glu	Arg	Arg	Phe	Leu	Lys	Ala	Pro	Leu	
	1205					1210					1215				
Asp	Ala	Ser	Asp	Ser	Gly	Arg	Ser	Tyr	Lys	Thr	Val	Leu	Asp	Arg	
	1220					1225					1230				

Trp	Arg	Glu	Ser	Leu	Leu	Ser	Ser	Ala	Ser	Leu	Ser	Gln	Val	Phe
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Leu	His	Leu	Ser	Thr	Leu	Asp	Arg	Ser	Val	Ile	Trp	Ser	Lys	Ser
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Ile	Leu	Asn	Ala	Arg	Cys	Lys	Ile	Cys	Arg	Lys	Lys	Gly	Asp	Ala
1265						1270					1275			
Glu	Asn	Met	Val	Leu	Cys	Asp	Gly	Cys	Asp	Arg	Gly	His	His	Thr
1280						1285					1290			
Tyr	Cys	Val	Arg	Pro	Lys	Leu	Lys	Thr	Val	Pro	Glu	Gly	Asp	Trp
1295						1300					1305			
Phe	Cys	Pro	Glu	Cys	Arg	Pro	Lys	Gln	Arg	Cys	Arg	Arg	Leu	Ser
1310						1315					1320			
Phe	Arg	Gln	Arg	Pro	Ser	Leu	Glu	Ser	Asp	Glu	Asp	Val	Glu	Asp
1325						1330					1335			
Ser	Met	Gly	Gly	Glu	Asp	Asp	Glu	Val	Asp	Gly	Asp	Glu	Glu	Glu
1340						1345					1350			
Gly	Gln	Ser	Glu	Glu	Glu	Glu	Tyr	Glu	Val	Glu	Gln	Asp	Glu	Asp
1355						1360					1365			
Asp	Ser	Gln	Glu	Glu	Glu	Glu	Val	Ser	Leu	Pro	Lys	Arg	Gly	Arg
1370						1375					1380			
Pro	Gln	Val	Arg	Leu	Pro	Val	Lys	Thr	Arg	Gly	Lys	Leu	Ser	Ser
1385						1390					1395			
Ser	Phe	Ser	Ser	Arg	Gly	Gln	Gln	Gln	Glu	Pro	Gly	Arg	Tyr	Pro
1400						1405					1410			
Ser	Arg	Ser	Gln	Gln	Ser	Thr	Pro	Lys	Thr	Thr	Val	Ser	Ser	Lys
1415						1420					1425			
Thr	Gly	Arg	Ser	Leu	Arg	Lys	Ile	Asn	Ser	Ala	Pro	Pro	Thr	Glu
1430						1435					1440			
Thr	Lys	Ser	Leu	Arg	Ile	Ala	Ser	Arg	Ser	Thr	Arg	His	Ser	His
1445						1450					1455			

Gly Pro Leu Gln Ala Asp Val Phe Val Glu Leu Leu Ser Pro Arg  
 1460 1465 1470  
 Arg Lys Arg Arg Gly Arg Lys Ser Ala Asn Asn Thr Pro Glu Asn  
 1475 1480 1485  
 Ser Pro Asn Phe Pro Asn Phe Arg Val Ile Ala Thr Lys Ser Ser  
 1490 1495 1500  
 Glu Gln Ser Arg Ser Val Asn Ile Ala Ser Lys Leu Ser Leu Gln  
 1505 1510 1515  
 Glu Ser Glu Ser Lys Arg Arg Cys Arg Lys Arg Gln Ser Pro Glu  
 1520 1525 1530  
 Pro Ser Pro Val Thr Leu Gly Arg Arg Ser Ser Gly Arg Gln Gly  
 1535 1540 1545  
 Gly Val His Glu Leu Ser Ala Phe Glu Gln Leu Val Val Glu Leu  
 1550 1555 1560  
 Val Arg His Asp Asp Ser Trp Pro Phe Leu Lys Leu Val Ser Lys  
 1565 1570 1575  
 Ile Gln Val Pro Asp Tyr Tyr Asp Ile Ile Lys Lys Pro Ile Ala  
 1580 1585 1590  
 Leu Asn Ile Ile Arg Glu Lys Val Asn Lys Cys Glu Tyr Lys Leu  
 1595 1600 1605  
 Ala Ser Glu Phe Ile Asp Asp Ile Glu Leu Met Phe Ser Asn Cys  
 1610 1615 1620  
 Phe Glu Tyr Asn Pro Arg Asn Thr Ser Glu Ala Lys Ala Gly Thr  
 1625 1630 1635  
 Arg Leu Gln Ala Phe Phe His Ile Gln Ala Gln Lys Leu Gly Leu  
 1640 1645 1650  
 His Val Thr Pro Ser Asn Val Asp Gln Val Ser Thr Pro Pro Ala  
 1655 1660 1665  
 Ala Lys Lys Ser Arg Ile  
 1670

<210> 110  
 <211> 1483

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 110

Met Ala Pro Leu Leu Gly Arg Lys Pro Phe Pro Leu Val Lys Pro Leu  
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Pro Gly Glu Glu Pro Leu Phe Thr Ile Pro His Thr Gln Glu Ala Phe  
 20 25 30

Arg Thr Arg Glu Glu Tyr Glu Ala Arg Leu Glu Arg Tyr Ser Glu Arg  
 35 40 45

Ile Trp Thr Cys Lys Ser Thr Gly Ser Ser Gln Leu Thr His Lys Glu  
 50 55 60

Ala Trp Glu Glu Glu Gln Glu Val Ala Glu Leu Leu Lys Glu Glu Phe  
 65 70 75 80

Pro Ala Trp Tyr Glu Lys Leu Val Leu Glu Met Val His His Asn Thr  
 85 90 95

Ala Ser Leu Glu Lys Leu Val Asp Thr Ala Trp Leu Glu Ile Met Thr  
 100 105 110

Lys Tyr Ala Val Gly Glu Glu Cys Asp Phe Glu Val Gly Lys Glu Lys  
 115 120 125

Met Leu Lys Val Lys Ile Val Lys Ile His Pro Leu Glu Lys Val Asp  
 130 135 140

Glu Glu Ala Thr Glu Lys Lys Ser Asp Gly Ala Cys Asp Ser Pro Ser  
 145 150 155 160

Ser Asp Lys Glu Asn Ser Ser Gln Ile Ala Gln Asp His Gln Lys Lys  
 165 170 175

Glu Thr Val Val Lys Glu Asp Glu Gly Arg Arg Glu Ser Ile Asn Asp  
 180 185 190

Arg Ala Arg Arg Ser Pro Arg Lys Leu Pro Thr Ser Leu Lys Lys Gly  
 195 200 205

Glu Arg Lys Trp Ala Pro Pro Lys Phe Leu Pro His Lys Tyr Asp Val  
 210 215 220

Lys Leu Gln Asn Glu Asp Lys Ile Ile Ser Asn Val Pro Ala Asp Ser



225		230		235		240
Leu Ile Arg Thr Glu Arg Pro Pro Asn Lys Glu Ile Val Arg Tyr Phe						
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Ile Arg His Asn Ala Leu Arg Ala Gly Thr Gly Glu Asn Ala Pro Trp						
	260		265		270	
Val Val Glu Asp Glu Leu Val Lys Lys Tyr Ser Leu Pro Ser Lys Phe						
	275		280		285	
Ser Asp Phe Leu Leu Asp Pro Tyr Lys Tyr Met Thr Leu Asn Pro Ser						
	290		295		300	
Thr Lys Arg Lys Asn Thr Gly Ser Pro Asp Arg Lys Pro Ser Lys Lys						
305		310		315		320
Ser Lys Thr Asp Asn Ser Ser Leu Ser Ser Pro Leu Asn Pro Lys Leu						
	325		330			335
Trp Cys His Val His Leu Lys Lys Ser Leu Ser Gly Ser Pro Leu Lys						
	340		345		350	
Val Lys Asn Ser Lys Asn Ser Lys Ser Pro Glu Glu His Leu Glu Glu						
	355		360		365	
Met Met Lys Met Met Ser Pro Asn Lys Leu His Thr Asn Phe His Ile						
	370		375		380	
Pro Lys Lys Gly Pro Pro Ala Lys Lys Pro Gly Lys His Ser Asp Lys						
385		390		395		400
Pro Leu Lys Ala Lys Gly Arg Ser Lys Gly Ile Leu Asn Gly Gln Lys						
	405		410		415	
Ser Thr Gly Asn Ser Lys Ser Pro Lys Lys Gly Leu Lys Thr Pro Lys						
	420		425		430	
Thr Lys Met Lys Gln Met Thr Leu Leu Asp Met Ala Lys Gly Thr Gln						
	435		440		445	
Lys Met Thr Arg Ala Pro Arg Asn Ser Gly Gly Thr Pro Arg Thr Ser						
	450		455		460	
Ser Lys Pro His Lys His Leu Pro Pro Ala Ala Leu His Leu Ile Ala						
465		470		475		480

Tyr Tyr Lys Glu Asn Lys Asp Arg Glu Asp Lys Arg Ser Ala Leu Ser  
 485 490 495  
 Cys Val Ile Ser Lys Thr Ala Arg Leu Leu Ser Ser Glu Asp Arg Ala  
 500 505 510  
 Arg Leu Pro Glu Glu Leu Arg Ser Leu Val Gln Lys Arg Tyr Glu Leu  
 515 520 525  
 Leu Glu His Lys Lys Arg Trp Ala Ser Met Ser Glu Glu Gln Arg Lys  
 530 535 540  
 Glu Tyr Leu Lys Lys Lys Arg Glu Glu Leu Lys Lys Lys Leu Lys Glu  
 545 550 555 560  
 Lys Ala Lys Glu Arg Arg Glu Lys Glu Met Leu Glu Arg Leu Glu Lys  
 565 570 575  
 Gln Lys Arg Tyr Glu Asp Gln Glu Leu Thr Gly Lys Asn Leu Pro Ala  
 580 585 590  
 Phe Arg Leu Val Asp Thr Pro Glu Gly Leu Pro Asn Thr Leu Phe Gly  
 595 600 605  
 Asp Val Ala Met Val Val Glu Phe Leu Ser Cys Tyr Ser Gly Leu Leu  
 610 615 620  
 Leu Pro Asp Ala Gln Tyr Pro Ile Thr Ala Val Ser Leu Met Glu Ala  
 625 630 635 640  
 Leu Ser Ala Asp Lys Gly Gly Phe Leu Tyr Leu Asn Arg Val Leu Val  
 645 650 655  
 Ile Leu Leu Gln Thr Leu Leu Gln Asp Glu Ile Ala Glu Asp Tyr Gly  
 660 665 670  
 Glu Leu Gly Met Lys Leu Ser Glu Ile Pro Leu Thr Leu His Ser Val  
 675 680 685  
 Ser Glu Leu Val Arg Leu Cys Leu Arg Arg Ser Asp Val Gln Glu Glu  
 690 695 700  
 Ser Glu Gly Ser Asp Thr Asp Asp Asn Lys Asp Ser Ala Ala Phe Glu  
 705 710 715 720  
 Asp Asn Glu Val Gln Asp Glu Phe Leu Glu Lys Leu Glu Thr Ser Glu

				725				730				735				
Phe	Phe	Glu	Leu	Thr	Ser	Glu	Glu	Lys	Leu	Gln	Ile	Leu	Thr	Ala	Leu	
			740					745					750			
Cys	His	Arg	Ile	Leu	Met	Thr	Tyr	Ser	Val	Gln	Asp	His	Met	Glu	Thr	
			755					760					765			
Arg	Gln	Gln	Met	Ser	Ala	Glu	Leu	Trp	Lys	Glu	Arg	Leu	Ala	Val	Leu	
			770					775					780			
Lys	Glu	Glu	Asn	Asp	Lys	Lys	Arg	Ala	Glu	Lys	Gln	Lys	Arg	Lys	Glu	
					790					795					800	
Met	Glu	Ala	Lys	Asn	Lys	Glu	Asn	Gly	Lys	Val	Glu	Asn	Gly	Leu	Gly	
				805					810					815		
Lys	Thr	Asp	Arg	Lys	Lys	Glu	Ile	Val	Lys	Phe	Glu	Pro	Gln	Val	Asp	
			820					825					830			
Thr	Glu	Ala	Glu	Asp	Met	Ile	Ser	Ala	Val	Lys	Ser	Arg	Arg	Leu	Leu	
			835					840					845			
Ala	Ile	Gln	Ala	Lys	Lys	Glu	Arg	Glu	Ile	Gln	Glu	Arg	Glu	Met	Lys	
			850					855					860			
Val	Lys	Leu	Glu	Arg	Gln	Ala	Glu	Glu	Glu	Arg	Ile	Arg	Lys	His	Lys	
			865					870					875			
Ala	Ala	Ala	Glu	Lys	Ala	Phe	Gln	Glu	Gly	Ile	Ala	Lys	Ala	Lys	Leu	
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Val	Met	Arg	Arg	Thr	Pro	Ile	Gly	Thr	Asp	Arg	Asn	His	Asn	Arg	Tyr	
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Trp	Leu	Phe	Ser	Asp	Glu	Val	Pro	Gly	Leu	Phe	Ile	Glu	Lys	Gly	Trp	
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Val	His	Asp	Ser	Ile	Asp	Tyr	Arg	Phe	Asn	His	His	Cys	Lys	Asp	His	
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Thr	Val	Ser	Gly	Asp	Glu	Asp	Tyr	Cys	Pro	Arg	Ser	Lys	Lys	Ala	Asn	
			945					950					955			
Leu	Gly	Lys	Asn	Ala	Ser	Met	Asn	Thr	Gln	His	Gly	Thr	Ala	Thr	Glu	
				965					970					975		

Val Ala Val Glu Thr Thr Thr Pro Lys Gln Gly Gln Asn Leu Trp Phe  
 980 985 990

Leu Cys Asp Ser Gln Lys Glu Leu Asp Glu Leu Leu Asn Cys Leu His  
 995 1000 1005

Pro Gln Gly Ile Arg Glu Ser Gln Leu Lys Glu Arg Leu Glu Lys  
 1010 1015 1020

Arg Tyr Gln Asp Ile Ile His Ser Ile His Leu Ala Arg Lys Pro  
 1025 1030 1035

Asn Leu Gly Leu Lys Ser Cys Asp Gly Asn Gln Glu Leu Leu Asn  
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Phe Leu Arg Ser Asp Leu Ile Glu Val Ala Thr Arg Leu Gln Lys  
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Gly Gly Leu Gly Tyr Val Glu Glu Thr Ser Glu Phe Glu Ala Arg  
 1070 1075 1080

Val Ile Ser Leu Glu Lys Leu Lys Asp Phe Gly Glu Cys Val Ile  
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Ala Leu Gln Ala Ser Val Ile Lys Lys Phe Leu Gln Gly Phe Met  
 1100 1105 1110

Ala Pro Lys Gln Lys Arg Arg Lys Leu Gln Ser Glu Asp Ser Ala  
 1115 1120 1125

Lys Thr Glu Glu Val Asp Glu Glu Lys Lys Met Val Glu Glu Ala  
 1130 1135 1140

Lys Val Ala Ser Ala Leu Glu Lys Trp Lys Thr Ala Ile Arg Glu  
 1145 1150 1155

Ala Gln Thr Phe Ser Arg Met His Val Leu Leu Gly Met Leu Asp  
 1160 1165 1170

Ala Cys Ile Lys Trp Asp Met Ser Ala Glu Asn Ala Arg Cys Lys  
 1175 1180 1185

Val Cys Arg Lys Lys Gly Glu Asp Asp Lys Leu Ile Leu Cys Asp  
 1190 1195 1200

Glu Cys Asn Lys Ala Phe His Leu Phe Cys Leu Arg Pro Ala Leu

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Tyr Glu Val Pro Asp Gly Glu Trp Gln Cys Pro Ala Cys Gln Pro				
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Ala Thr Ala Arg Arg Asn Ser Arg Gly Arg Asn Tyr Thr Glu Glu				
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Ser Ala Ser Glu Asp Ser Glu Asp Asp Glu Ser Asp Glu Glu Glu				
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Glu Glu Glu Glu Glu Glu Glu Glu Glu Asp Tyr Glu Val Ala				
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Gly Leu Arg Leu Arg Pro Arg Lys Thr Ile Arg Gly Lys His Ser				
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Val Ile Pro Pro Ala Ala Arg Ser Gly Arg Arg Pro Gly Lys Lys				
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Pro His Ser Thr Arg Arg Ser Gln Pro Lys Ala Pro Pro Val Asp				
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Asp Ala Glu Val Asp Glu Leu Val Leu Gln Thr Lys Arg Ser Ser				
1325		1330		1335
Arg Arg Gln Ser Leu Glu Leu Gln Lys Cys Glu Glu Ile Leu His				
1340		1345		1350
Met Ile Val Lys Tyr Arg Phe Ser Trp Pro Phe Arg Glu Pro Val				
1355		1360		1365
Thr Arg Asp Glu Ala Glu Asp Tyr Tyr Asp Val Ile Thr His Pro				
1370		1375		1380
Met Asp Phe Gln Thr Val Gln Asn Lys Cys Ser Cys Gly Ser Tyr				
1385		1390		1395
Arg Ser Val Gln Glu Phe Leu Thr Asp Met Lys Gln Val Phe Thr				
1400		1405		1410
Asn Ala Glu Val Tyr Asn Cys Arg Gly Ser His Val Leu Ser Cys				
1415		1420		1425
Met Val Lys Thr Glu Gln Cys Leu Val Ala Leu Leu His Lys His				
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Leu Pro Gly His Pro Tyr Val Arg Arg Lys Arg Lys Lys Phe Pro  
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Asp Arg Leu Ala Glu Asp Glu Gly Asp Ser Glu Pro Glu Ala Val  
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Gly Gln Ser Arg Gly Arg Arg Gln Lys Lys  
 1475 1480

<210> 111  
 <211> 526  
 <212> PRT  
 <213> Homo sapiens

<400> 111

Met Val Met Lys Ala Ser Val Asp Asp Asp Asp Ser Gly Trp Glu Leu  
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Ser Met Pro Glu Lys Met Glu, Lys Ser Asn Thr Asn Trp Val Asp Ile  
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Thr Gln Asp Phe Glu Glu Ala Cys Arg Glu Leu Lys Leu Gly Glu Leu  
 35 40 45

Leu His Asp Lys Leu Phe Gly Leu Phe Glu Ala Met Ser Ala Ile Glu-  
 50 55 60

Met Met Asp Pro Lys Met Asp Ala Gly Met Ile Gly Asn Gln Val Asn  
 65 70 75 80

Arg Lys Val Leu Asn Phe Glu Gln Ala Ile Lys Asp Gly Thr Ile Lys  
 85 90 95

Ile Lys Asp Leu Thr Leu Pro Glu Leu Ile Gly Ile Met Asp Thr Cys  
 100 105 110

Phe Cys Cys Leu Ile Thr Trp Leu Glu Gly His Ser Leu Ala Gln Thr  
 115 120 125

Val Phe Thr Cys Leu Tyr Ile His Asn Pro Asp Phe Ile Glu Asp Pro  
 130 135 140

Ala Met Lys Ala Phe Ala Leu Gly Ile Leu Lys Ile Cys Asp Ile Ala  
 145 150 155 160

Arg Glu Lys Val Asn Lys Ala Ala Val Phe Glu Glu Glu Asp Phe Gln  
 165 170 175

Ser Met Thr Tyr Gly Phe Lys Met Ala Asn Ser Val Thr Asp Leu Arg  
 180 185 190

Val Thr Gly Met Leu Lys Asp Val Glu Asp Asp Met Gln Arg Arg Val  
 195 200 205

Lys Ser Thr Arg Ser Arg Gln Gly Glu Glu Arg Asp Pro Glu Val Glu  
 210 215 220

Leu Glu His Gln Arg Cys Leu Ala Val Phe Ser Arg Val Lys Phe Thr  
 225 230 235 240

Arg Val Leu Leu Thr Val Leu Ile Ala Phe Thr Lys Lys Glu Thr Ser  
 245 250 255

Ala Val Ala Glu Ala Gln Lys Leu Met Val Gln Ala Ala Asp Leu Leu  
 260 265 270

Ser Ala Ile His Asn Ser Leu His His Gly Ile Gln Ala Gln Asn Asp  
 275 280 285

Thr Thr Lys Gly Asp His Pro Ile Met Met Gly Phe Glu Pro Leu Val  
 290 295 300

Asn Gln Arg Leu Leu Pro Pro Thr Phe Pro Arg Tyr Ala Lys Ile Ile  
 305 310 315 320

Lys Arg Glu Glu Met Val Asn Tyr Phe Ala Arg Leu Ile Asp Arg Ile  
 325 330 335

Lys Thr Val Cys Glu Val Val Asn Leu Thr Asn Leu His Cys Ile Leu  
 340 345 350

Asp Phe Phe Cys Glu Phe Ser Glu Gln Ser Pro Cys Val Leu Ser Arg  
 355 360 365

Ser Leu Leu Gln Thr Thr Phe Leu Val Asp Asn Lys Lys Val Phe Gly  
 370 375 380

Thr His Leu Met Gln Asp Met Val Lys Asp Ala Leu Arg Ser Phe Val  
 385 390 395 400

Ser Pro Pro Val Leu Ser Pro Lys Cys Tyr Leu Tyr Asn Asn His Gln  
 405 410 415

Ala Lys Asp Cys Ile Asp Ser Phe Val Thr His Cys Val Arg Pro Phe  
 420 425 430

Cys Ser Leu Ile Gln Ile His Gly His Asn Arg Ala Arg Gln Arg Asp  
 435 440 445

Lys Leu Gly His Ile Leu Glu Glu Phe Ala Thr Leu Gln Asp Glu Ala  
 450 455 460

Glu Lys Val Asp Ala Ala Leu His Thr Met Leu Leu Lys Gln Glu Pro  
 465 470 475 480

Gln Arg Gln His Leu Ala Trp Leu Gly Thr Trp Val Leu Tyr His Asn  
 485 490 495

Leu Arg Ile Met Ile Gln Tyr Leu Leu Ser Gly Phe Glu Leu Glu Leu  
 500 505 510

Tyr Ser Met His Glu Ile Leu Leu His Ile Leu Val Ser Leu  
 515 520 525

<210> 112  
 <211> 368  
 <212> PRT  
 <213> Homo sapiens

<400> 112

Met Ala Ala Ala Ala Glu Glu Arg Met Ala Glu Glu Gly Gly Gly Gly  
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Gln Gly Asp Gly Gly Ser Ser Leu Ala Ser Gly Ser Thr Gln Arg Gln  
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Pro Pro Pro Pro Ala Pro Gln His Pro Gln Pro Gly Ser Gln Ala Leu  
 35 40 45

Pro Ala Pro Ala Leu Ala Pro Asp Gln Leu Pro Gln Asn Asn Thr Leu  
 50 55 60

Val Ala Leu Pro Ile Val Ala Ile Glu Asn Ile Leu Ser Phe Met Ser  
 65 70 75 80

Tyr Asp Glu Ile Ser Gln Leu Arg Leu Val Cys Lys Arg Met Asp Leu  
 85 90 95

Val Cys Gln Arg Met Leu Asn Gln Gly Phe Leu Lys Val Glu Arg Tyr  
 100 105 110



His Asn Leu Cys Gln Lys Gln Val Lys Ala Gln Leu Pro Arg Arg Glu  
 115 120 125

Ser Glu Arg Arg Asn His Ser Leu Ala Arg His Ala Asp Ile Leu Ala  
 130 135 140

Ala Val Glu Thr Arg Leu Ser Leu Leu Asn Met Thr Phe Met Lys Tyr  
 145 150 155 160

Val Asp Ser Asn Leu Cys Cys Phe Ile Pro Gly Lys Val Ile Asp Glu  
 165 170 175

Ile Tyr Arg Val Leu Arg Tyr Val Asn Ser Thr Arg Ala Pro Gln Arg  
 180 185 190

Ala His Glu Val Leu Gln Glu Leu Arg Asp Ile Ser Ser Met Ala Met  
 195 200 205

Glu Tyr Phe Asp Glu Lys Ile Val Pro Ile Leu Lys Arg Lys Leu Pro  
 210 215 220

Gly Ser Asp Val Ser Gly Arg Leu Met Gly Ser Pro Pro Val Pro Gly  
 225 230 235 240

Pro Ser Ala Ala Leu Thr Thr Met Gln Leu Phe Ser Lys Gln Asn Pro  
 245 250 255

Ser Arg Gln Glu Val Thr Lys Leu Gln Gln Gln Val Lys Thr Asn Gly  
 260 265 270

Ala Gly Val Thr Val Leu Arg Arg Glu Ile Ser Glu Leu Arg Thr Lys  
 275 280 285

Val Gln Glu Gln Gln Lys Gln Leu Gln Asp Gln Asp Gln Lys Leu Leu  
 290 295 300

Glu Gln Thr Gln Ile Ile Gly Glu Gln Asn Ala Arg Leu Ala Glu Leu  
 305 310 315 320

Glu Arg Lys Leu Arg Glu Val Met Glu Ser Ala Val Gly Asn Ser Ser  
 325 330 335

Gly Ser Gly Gln Asn Glu Glu Ser Pro Arg Lys Arg Lys Lys Ala Thr  
 340 345 350

Glu Ala Ile Asp Ser Leu Arg Lys Ser Lys Arg Leu Arg Asn Arg Lys

355

360

365

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